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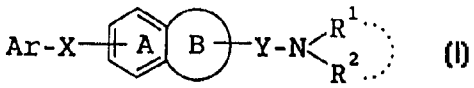

(I)

(57) Abstract

A compound of formula (I) wherein Ar is an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted; X is (i) a bond, (ii) –S–, –SO– or –SO_2–, (iii) C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene, etc., (iv) –CO–O– or (v) –(CH_2)p–x^1–, –(CH_2)p–X^1–(CH_2)q–, –(CH_2)r–CO–X^1–, –SO_2–NR^8– or –(CH_2)r–SO_2–NR^8– wherein X^1 is O or NR^8, R^8 is H, a hydrocarbon group which may be substituted or an acyl, p is 0 to 5, q is 1 to 5, p+q is 1 to 5, and r is 1 to 4; Y is a divalent C_{1-6} aliphatic hydrocarbon group optionally containing O or S, which may be substituted; R^1 and R^2 each is H or a lower alkyl which may be substituted, or R^1 and R^2 form an N–containing heterocyclic ring which may be substituted; Ring A is a benzene ring which may be further substituted; and Ring B is a 4– to 8–membered ring which may be further substituted, or a salt thereof has the effect of inhibiting amyloid–β protein production and/or secretion and is useful as a pharmaceutical composition for preventing and/or treating the neurodegenerative disease, etc.

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DESCRIPTION

AMINE COMPOUNDS, THEIR PRODUCTION AND USE AS AMYLOID-BETA PRODUCTION INHIBITORS

TECHNICAL FIELD

The present invention relates to an amine compound having an excellent effect of inhibiting production and/or secretion of amyloid-β protein, a production and use thereof. Especially, it is effective for preventing and/or treating, for example, neurodegenerative diseases, amyloid angiopathy, neurological disorders caused by cerebrovascular disorders, and so forth.

BACKGROUND ART

Alzheimer's disease is a neurodegenerative disease, which is characterized by the degeneration and loss of neuronal cells accompanied by the formation of senile plaques and neurofibrillary tangles. Senile plaque that is the most characteristic in Alzheimer's disease consist of essentially amyloid-β protein (hereinafter referred to as Aβ) [see Biochem. Biophys. Res. Commun., 122, 1311 (1984)] and other intracerebral components. It is known that Aβ comprised of 40 or 42 amino acids (hereinafter referred to as $A\beta_{1-40}$ and $A\beta_{1-42}$, respectively) is toxic to neurons and induces neurofibrillary changes.

Some patients with familial Alzheimer's disease are known to have APP (amyloid precursor protein) gene mutation, and it is well known that the cells transfected with such mutated gene produce and secrete an increased amount of Aβ [for example, see Nature, 360, 672 (1992); Science, 259, 514 (1993); Science, 264, 1336 (1994), etc.].

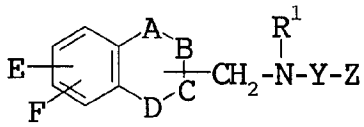
Based on the information, medicines which inhibit production and/or secretion are useful for preventing and/or treating diseases caused by Aβ (e.g., Alzheimer's disease, Down's syndrome, etc).

Alternatively, secreted form of amyloid precursor protein (sAPP) is reported to have neurotrophic factor like property (Neuron, 10, 243-254,1993). As neurotrophic factor like property, 1) survival and preserving effect to the neuronal cell; 2) stimulating the synapse formation; 3) protection of neuronal cell death; and 4) long term potentiation in hippocampus are given as examples. By the above-mentioned property, drugs which stimulate the sAPP secretion are also useful in preventing and treating 1) neurodegenerative diseases such as dementia (e.g., senile dementia, amnesia, etc.), Alzheimer's disease, Down's syndrome, Parkinson's disease, Creutzfeldt-Jacob disease, amyotrophic sclerosis on lateral fasciculus, Huntington's disease, multiple sclerosis, etc., 2) neurological disorders involved in cerebrovascular disorders (e.g., cerebral infarction, encephalorrhagia, etc.), a head injury or an injury of spinal cord, and so forth.

EP-A-652009 discloses peptide derivatives which is a protease inhibitor exhibiting an Aβ production inhibiting effect in *in vitro* experiments using cell lines.

On the other hand, the following bicyclic amine compounds are known.

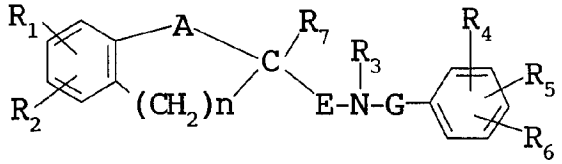
1) JP-A-2-96552 (USP 5,137,901) discloses a compound of the formula:



wherein Y represents a straight-chain or branched,

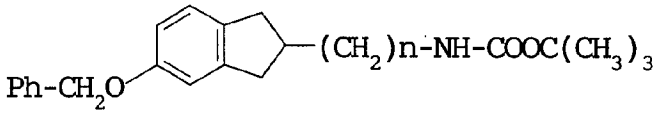
substituted or unsubstituted alkylene chain having up to 6 carbon atoms; Z represents a group of the formula: $-NR^2R^3$, $-OR^4$, or the like; R^2 and R^3 are identical or different and represent hydrogen, alkyl, alkenyl or cycloalkyl, or represent aryl which may be substituted by halogen, etc.; R^4 represents hydrogen, alkyl, alkenyl, or the like; R^1 represents hydrogen, alkyl, aralkyl, heteroarylalkyl or a group of the formula: $-(Y^1-Z^1)$ in which Y^1 and Z^1 are identical or different and have the same meanings as Y and Z; A and D each represents a group of the formula: $-CH_2$, O, S or NR^{13}, or the moiety of -CH or N of a double bond C=C or C=NH, with the proviso that either only A or only D represents oxygen, sulfur or $N-R^{13}$; R^{13} represents hydrogen, alkyl, alkoxy, acyl, alkoxycarbonyl or alkylsulfonyl; B represents a group of the formula: $-CH_2$ or $\geqslant CH$ or the moiety of -CH or N of a double bond C=C or C=N; C represents a group of the formula: $\geqslant CH$, or the moiety of C of a double bond C=C or C=N; E and F are identical or different and each represents hydrogen, alkyl, alkoxy, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy or a group of the formula: $-CONR^2R^3$ in which R^2 and R^3 have the same meanings as above, or E and F together form a substituted or unsubstituted carbocycle having 6 carbon atoms, which is agonist, partial agonist and antagonist on the serotonin receptors and is suitable for the treatment of central nervous system disorders, etc.

2) JP-A-63-77842 discloses a compound of the formula:



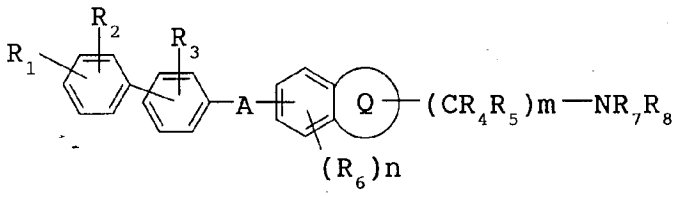
wherein n represents 1 or 2; A represents a carbonyl while R_7 is hydrogen, or A represents a group of the formula: $-CHR_8-$ wherein R_8 represents hydrogen, alkanoyloxy or alkoxycarbonyl, while R_7 is hydrogen or R_7 and R_8 together form another bond; E represents a straight-chain alkylene which has 3 or 4 carbon atoms and may be substituted by an alkyl; G represents a straight-chain alkylene which has 2 to 5 carbon atoms and may be substituted by an alkyl; R_1 represents hydrogen, trifluoromethyl, nitro, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy or phenylalkoxy; R_2 represents hydrogen, halogen atoms, hydroxy, alkoxy, phenylalkoxy or alkyl; or R_1 and R_2 together form an alkylenedioxy having 1 or 2 carbon atoms; R_3 represents hydrogen, alkenyl or alkyl having 3 to 5 carbon atoms; R_4 represents hydrogen, halogen atoms, alkyl, or the like; R_5 represents hydrogen, halogen atoms, alkyl, or the like; and R_6 represents hydrogen, halogen atoms, alkyl, or the like, which is suitable for the treatment of sinus tachycardia and also for the prevention and treatment of ischemic heart disease because of its pharmacological action, decrease in the heart rate and oxygen demand of the heart.

3) WO 92/15558 discloses a compound of the formula:



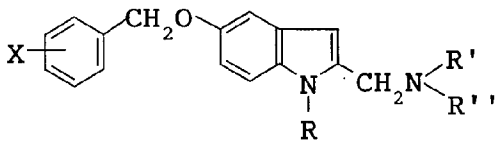
wherein n represents an integer of 1 to 4, which is an intermediate of a compound having a thromboxane A_2 antagonistic effect.

4) WO 95/32967 discloses amide derivatives of the formula:



wherein A is CONR where R is hydrogen or C_{1-6} alkyl; Q is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R_1 is hydrogen, halogen, etc.; R_2 and R_3 are independently hydrogen, halogen, etc.; R_4 and R_5 are independently hydrogen or C_{1-6} alkyl; R_6 is halogen, hydroxy, etc.; R_7 and R_8 are independently hydrogen, C_{1-6} alkyl, aralkyl, or together with the nitrogen atom to which they are attached from an optionally substituted 5 to 7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur; m is 0 to 4; and n is 0, 1 or 2, which has $5HT_{1D}$ receptor antagonist activity and is useful for the treatment of various CNS disorders.

5) EP-A-754455 discloses a pharmaceutical compositions for the therapeutic application as neuroprotectors in Parkinson's and Alzheimer's diseases containing a compound of the formula:



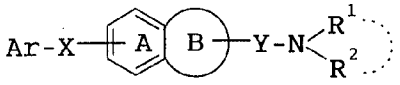
wherein X is H, halogen, alkoxy, alkyl, alkylthio, aryl, aryloxy; R is H, CH_3 or other aliphatic, alicyclic or aryl radicals; R' is H, CH_3 or other aliphatic or alicyclic C_1-C_3 radicals, or an aryl or arylalkyl, or a radical the same as those indicated for R''; and R'' is H, CH_3 or other aliphatic or alicyclic C_1-C_3 radicals, or an aryl or arylalkyl, or an acetylene or allene

group, being potent selective monoamine oxydase B inhibitors.

The conventional Aβ production inhibitors for the treatment of Alzheimer's disease are problematic in their oral absorbability, stability, etc. and are therefore unsatisfactory as medicines. It is desired to develop a compound which is different from the known compounds mentioned above in its chemical structure and which have an excellent inhibitory effect on Aβ production and/or secretion and is therefore satisfactorily used in medicines.

DISCLOSURE OF INVENTION

We, the present inventors have studied various compounds having an inhibitory effect on Aβ production and/or secretion and, as a result, have succeeded in, for the first time, the production of novel a compound of the formula:

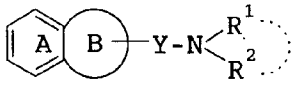


(I)

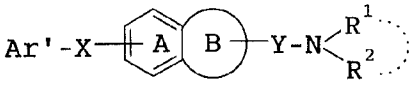
wherein Ar represents an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted;

X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$ wherein X^1 represents O (oxygen atom) or NR^8, R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5,

p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;
Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;
R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or
R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;
Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and
Ring B represents a 4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above;
provided that, when the fused ring to be formed by Ring A and Ring B is an indole ring, the group of the formula: -X-Ar wherein each symbol is as defined above is substituted on 4-, 6- or 7-position of the indole ring, or a salt thereof [hereinafter sometimes referred to as compound (I)], which is characterized by the chemical structure in that the benzene ring A of the skeleton of the formula:



wherein the symbols have the same meanings as above, is substituted by the group of the formula: -X-Ar wherein the symbols have the same meanings as above. We have found for the first time that compound (I), being based on its specific chemical structure, has an unexpected, excellent inhibitory effect on Aβ production and/or secretion, that a compound of the formula:

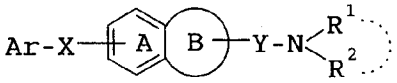


(I')

wherein Ar' represents an aromatic group which may be substituted, and the other symbols have the same meanings as above, or salt thereof [hereinafter sometimes referred to as compound (I')] also has an unexpected, excellent inhibitory effect on Aβ production and/or secretion, and that those compounds have low toxicity and are therefore satisfactory as medicines. Compound (I) is within the scope of compound (I'). On the basis of these findings, the inventors have completed the present invention.

Specifically, the present invention relates to:

(1) a compound of the formula:



wherein Ar represents an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted;

X represents a chemical bond or a spacer of which the number of atoms constituting the principal chain is 1 to 6;

Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;

R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;

Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B represents a 4- to 8-membered ring which may be

further substituted apart from the group of the formula: -Y-NR^1R^2 wherein each symbol is as defined above;

provided that, when the fused ring to be formed by Ring A and Ring B is an indole ring, the group of the formula: -X-Ar wherein each symbol is as defined above is substituted on 4-, 6- or 7-position of the indole ring, or a salt thereof;

(2) compound (I), wherein

Ar is (i) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which rings are directly bonded to each other via a single bond, and which assembly group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and

C_{6-10} aryloxy, or

(ii) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy;

R^8 is (a) a hydrogen atom,

(b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino,

(13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle-carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an

aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6}

alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

(c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl;

Y is a C_{1-6} alkylene, a C_{2-6} alkenylene, a C_{2-6} alkynylene or a group of the formula: $-(CH_2)m-Y^1-(CH_2)n-$ wherein $-Y^1-$ is -O-, -S-, -SO- or $-SO_2-$,

m is an integer of 0 to 4,

n is an integer of 1 to 5, and

m+n is an integer of 1 to 5;

R^1 and R^2 each is a hydrogen atom or a C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6}

alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy, C_{6-10} aryloxy and C_{6-10} aryl or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a 3- to 8-membered nitrogen-containing heterocyclic ring having one nitrogen atom and optionally having 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which ring may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10}

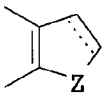
aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally

halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-

carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (21) an oxo and (22) C_{7-19} aralkyl;

Ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, hydroxy and amino, apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B is a 4- to 8-membered ring of the formula:



wherein --- is a single bond or a double bond, and Z is (i) a bond, (ii) a C_{1-4} alkylene, (iii) a C_{2-4} alkenylene, (iv) -O-CH_2-, (v) -O-CH_2-CH_2- or (vi) a group of the formula: -NR^{8a}-CH_2- or -NR^{8a}-CH_2-CH_2- wherein R^{8a} is (a) a hydrogen atom, (b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10}

arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon

atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6}

alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or (c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, which ring may be further substituted by 1 to 3 substituents selected from the group consisting of oxo, C_{1-6} alkyl and hydroxy, apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above;

(3) compound (I), wherein Ar is an aromatic ring assembly group which may be substituted;

(4) a compound of the above (3), wherein the aromatic rings of the aromatic ring assembly group are two or three aromatic rings selected from the group consisting of benzene, thiophene, pyridine, pyrimidine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, naphthalene, and benzofuran;

(5) a compound of the above (3), wherein the aromatic ring assembly group is 2-, 3- or 4-biphenylyl;

(6) compound (I), wherein Ar is a 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6}

alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy;

(7) compound (I), wherein X is a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom;

(8) compound (I), wherein X is a C_{1-6} alkylene;

(9) compound (I), wherein X is a group of the formula: $-(CH_2)p-X^1-$ wherein each symbol is as defined above;

(10) a compound of the above (9), wherein p is 1;

(11) a compound of the above (10), wherein X^1 is O;

(12) a compound of the above (10), wherein X^1 is NR^{8b} wherein R^{8b} is hydrogen or C_{1-6} alkyl-carbonyl;

(13) compound (I), wherein X^1 is a group of the formula: $-SO_2-NR^8-$ wherein each symbol is as defined above;

(14) a compound of the above (13), wherein R^8 is hydrogen;

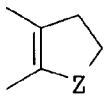
(15) compound (I), wherein Y is a divalent C_{1-6} aliphatic hydrocarbon group;

(16) compound (I), wherein Y is C_{1-6} alkylene;

(17) compound (I), wherein R^1 and R^2 each is C_{1-6} alkyl;

(18) compound (I), wherein Ring A is a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol is as defined above;

(19) compound (I), wherein Ring B is a 4- to 8-membered ring of the formula:



wherein Z is (i) a bond, (ii) a C_{1-4} alkylene, (iii) a C_{2-4} alkenylene, (iv) $-O-CH_2-$, (v) $-O-CH_2-CH_2-$ or (vi) a group of the formula: $-NR^{8a}-CH_2-$ or $-NR^{8a}-CH_2-CH_2-$ wherein R^{8a} is (a) a hydrogen atom, (b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group

containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-

membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

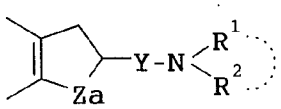
(c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl,

which ring may be further substituted by 1 to 3 substituents selected from the group consisting of oxo, C_{1-6} alkyl and hydroxy, apart from the group of the formula: -Y-NR^1R^2 wherein each symbol is as defined above;

(20) a compound of the above (19), wherein R^{8a} is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl;

(21) compound (I), wherein Ring B is a 6-membered carbocyclic or heterocyclic ring substituted by a group of the formula: -Y-NR^1R^2 wherein each symbol is as defined above;

(22) compound (I), wherein Ring B is a ring of the formula:

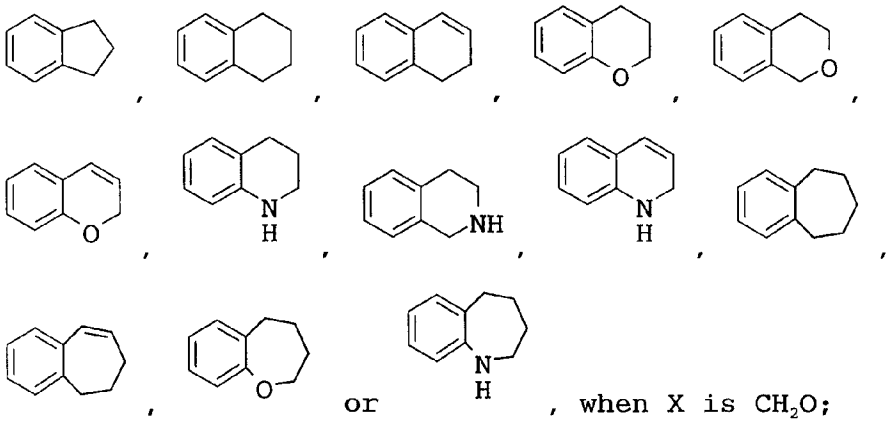


wherein Za is C_{1-3} alkylene or a group of the formula: -NR^{8c}-CH_2- wherein R^{8c} is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered

heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl;

(23) a compound of the above (22), wherein Za is ethylene;

(24) compound (I), wherein the fused ring to be formed by Ring A and Ring B is a ring of the formula:



when X is CH_2O;

(25) compound (I), wherein Ar is 2-, 3- or 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido;

X is C_{1-3} alkylene which may contain an oxygen atom;

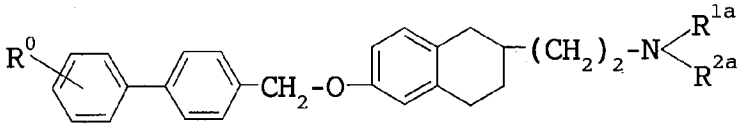
Y is C_{1-6} alkylene;

R^1 and R^2 each is C_{1-6} alkyl;

Ring A is a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B is a 6-membered carbocyclic or heterocyclic ring substituted by the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above;

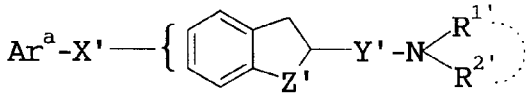
(26) compound (I), which is a compound of the formula:



wherein R^0 is 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido; and

R^{1a} and R^{2a} each is C_{1-6} alkyl, or a salt thereof;

(27) compound (I), which is a compound of the formula:



wherein Ar^a is (i) 2, 3- or 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, amino, formyl and C_{1-6} alkyl-carboxamido, (ii) 4-(2-thienyl)phenyl or 4-(3-thienyl)phenyl, (iii) 4-(3-pyridyl)phenyl, (iv) 6-phenyl-3-pyridyl which may be substituted by a C_{1-6} alkoxy, (v) 5-phenyl-1,3,4-oxadiazol-2-yl, (vi) 4-(2-naphthyl)phenyl, (vii) 4-(2-benzofuranyl)phenyl, (viii) 1- or 2-naphthyl, (ix) 2-quinolyl, (x) 2-benzothiazolyl or (xi) 2-benzofuranyl;

X' is $-CH_2-O-$, $-SO_2-NH-$ or a group of the formula: $-CH_2-NR^{8'}-$ wherein $R^{8'}$ is hydrogen or C_{1-3} alkyl-carbonyl;

Y' is C_{1-6} alkylene;

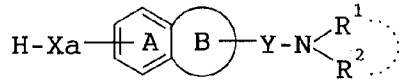
Z' is $-CH_2-CH_2-$ or a group of the formula: $-NR^{8''}-CH_2-$ wherein $R^{8''}$ is hydrogen, C_{1-3} alkyl, C_{1-3} alkyl-carbonyl or C_{1-3} alkylsulfonyl; and

$R^{1'}$ and $R^{2'}$ each is C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of di-C_{1-3} alkylamino, C_{1-3} alkoxy-carbonyl and phenyl, or

$R^{1'}$ and $R^{2'}$ form, taken together with the adjacent nitrogen atom, a pyrrolidin-1-yl, piperidino or piperazin-1-yl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, C_{1-3} alkoxy-carbonyl, piperidino, phenyl and benzyl, or a salt thereof;

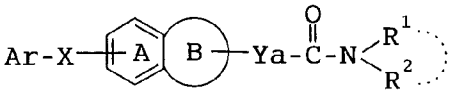
(28) compound (I) which is
6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
6-(4-biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin,
2-(N,N-dimethylamino)methyl-6-(4'-methoxybiphenyl-4-yl)methoxytetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methylbiphenyl-4-yl)methoxytetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methoxybiphenyl-4-yl)methoxytetralin,
(+)-6-(2',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-[4-(1,3-benzodioxol-5-yl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, or
(+)-6-(3',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, or a salt thereof;

(29) a process for producing of compound (I), which comprises;
i) subjecting a compound of the formula:



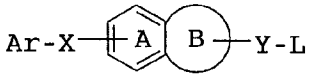
wherein Xa represents an oxygen atom, a sulfur atom which may be oxidized or a group of the formula: NR^8 wherein R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl; and the other symbols have the same meanings as above, or a salt thereof, to alkylation or acylation and optionally followed by aryl-coupling of the resultant compound;

ii) subjecting a compound of the formula:



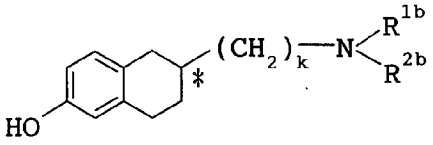
wherein Ya represents a group to be formed by removing a methylene from Y; and the other symbols have the same meanings as above, or a salt thereof, to reduction; or

iii) subjecting a compound of the formula:



wherein L represents a leaving group; and the other symbols have the same meanings as above, to amination;

(30) an optical isomer of the compound of the formula:



wherein R^{1b} and R^{2b} each represents methyl or ethyl, k represents 1 or 2, and * indicates the position of the asymmetric carbon, or a salt thereof;

(31) a pharmaceutical composition which comprises compound (I);

(32) a pharmaceutical composition of the above (31) which is an inhibitor for production and/or secretion of amyloid-β protein;

(33) a pharmaceutical composition of the above (31) which is for preventing and/or treating neurodegenerative diseases caused by amyloid-β protein;

(34) a pharmaceutical composition of the above (32), wherein the neurodegenerative disease caused by amyloid-β protein is Alzheimer's disease;

(35) a method of inhibiting production and/or secretion of amyloid-β protein in mammal, which comprises administering to said mammal an effective amount of compound (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent;

(36) a use of compound (I) for manufacturing a pharmaceutical composition for inhibiting production and/or secretion of amyloid-β protein;

(37) an inhibitor for production and/or secretion of amyloid-β protein, which comprises compound (I');

(38) a method of inhibiting production and/or secretion of amyloid-β protein in mammal, which comprises administering to said mammal an effective amount of compound (I') or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent;

(39) a use of compound (I') for manufacturing a pharmaceutical composition for inhibiting production and/or secretion of amyloid-β protein, and so forth.

In the above-mentioned formulae, the "aromatic ring assembly group" of the "aromatic ring assembly group which may be substituted" for Ar is meant to indicate a group which is derived, by removing an optional hydrogen atom from an assembled aromatic ring in which two or more, preferably two or three aromatic rings are directly joined to each other by single

bond(s) and the number of such direct ring junctions is one less than the number of the aromatic rings involved. The "aromatic ring" includes, for example, an aromatic hydrocarbon, an aromatic heterocyclic ring, etc.

The "aromatic hydrocarbon" includes, for example, a C_{6-14} monocyclic or fused polycyclic (preferably, bi- or tri-cyclic) aromatic hydrocarbon compound (e.g., benzene, naphthalene, indene, anthracene, etc.) or a C_{6-14} quinone (e.g., p-benzoquinone, 1,4-naphthoquinone, indan-4,7-dione, etc.), etc.

The "aromatic heterocyclic ring" includes, for example, 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic rings containing one or more (e.g., 1 to 4) hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, etc. Concretely mentioned is an aromatic heterocyclic ring, such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, phenoxathiin, pyrrole, imidazole, pyrazole, oxadiazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine, phthalimide, etc.; and a ring as formed through condensation of the above ring, preferably monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The assembly of those aromatic rings in which the rings are directly bonded to each other via a single bond includes, for example, those to be composed of two or three, preferably two aromatic rings selected from

the group consisting of benzene ring, naphthalene ring and 5- to 10-membered (preferably 5- or 6-membered) aromatic heterocyclic ring. As specific examples of the assembly of such aromatic rings, mentioned are biphenyl, 2-phenylnaphthalene, p-terphenyl, o-terphenyl, m-terphenyl, 2-phenylpyridine, 3-phenylpyridine, 4-phenylpyridine, 2-phenylthiophene, 3-phenylthiophene, 2-phenylindole, 3-phenylindole, 5-phenyl-1,3,4-oxadiazole, etc. Among others, preferred is an assembly which is composed of two or three aromatic rings selected from the group consisting of benzene, thiophene, pyridine, pyrimidine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, naphthalene and benzofuran.

Specific examples of the above "aromatic ring assembly group" are 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 4-(2-thienyl)phenyl, 4-(3-thienyl)phenyl, 3-(3-pyridyl)phenyl, 4-(3-pyridyl)phenyl, 6-phenyl-3-pyridyl, 5-phenyl-1,3,4-oxadiazol-2-yl, 4-(2-naphthyl)phenyl, 4-(2-benzofuranyl)phenyl, etc. Of those, preferred are 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, etc. , especially preferred is 4-biphenylyl.

The "substituent" for the "aromatic ring assembly group which may be substituted" includes, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 7-membered saturated cyclic amino, acyl, acylamino, acyloxy, C_{6-10} aryloxy (e.g., phenyloxy, naphthyloxy, etc.), and so forth.

The "aromatic ring assembly group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the aromatic ring assembly group, and when the number of substituents is two or more, those substituents may be the same as or different from one another.

The above-mentioned "optionally halogenated C_{1-6} alkyl" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Thus, for example, methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc. can be mentioned.

The above-mentioned "optionally halogenated C_{3-6} cycloalkyl" includes, for example, C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Thus, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc. can be mentioned.

The above-mentioned "optionally halogenated C_{1-6} alkoxy" includes, for example, C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Thus, for example, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy,

pentyloxy, hexyloxy, etc. can be mentioned.

The above-mentioned "optionally halogenated C_{1-6} alkylthio" includes, for example, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Thus, for example, methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc. can be mentioned.

The above-mentioned "5- to 7-membered saturated cyclic amino" includes, for example, morpholino, thiomorpholino, piperazin-1-yl, 4-substituted piperazin-1-yl, piperidino, pyrrolidin-1-yl, hexamethyleneimin-1-yl, etc.

The "substituent" for the "4-substituted piperazin-1-yl" includes, for example, C_{1-6} alkyl, C_{6-14} aryl which may be substituted, C_{7-19} aralkyl which may be substituted, 5- to 10-membered aromatic heterocyclic group which may be substituted, acyl, and so forth.

The "C_{6-14} aryl" of the "C_{6-14} aryl which may be substituted" includes, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc. Preferred is phenyl.

The "C_{7-19} aralkyl" of the "C_{7-19} aralkyl which may be substituted" includes, for example, benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc. Preferred is benzyl, etc.

The "5- to 10-membered aromatic heterocyclic group" of the "5- to 10-membered aromatic heterocyclic group which may be substituted" includes, for example, 2-, 3- or 4-pyridyl, 1-, 2- or 3-indolyl, 2- or 3-thienyl, etc. Preferred is 2-, 3- or 4-pyridyl, etc.

The "substituent" which those "C_{6-14} aryl which may be substituted", "C_{7-19} aralkyl which may be substituted" and "5- to 10-membered aromatic heterocyclic group which may be substituted" respectively may have, includes, for example, 1 to 5 substituents selected from the group consisting of halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), carboxy, and so forth.

The "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio" include those described above, respectively.

The "acyl" of (i) "acyl" exemplified as substituents for the above "4-substituted piperazin-1-yl", (ii) "acyl" exemplified as substituents for the above "aromatic ring assembly group which may be substituted", (iii) the above "acylamino" and (iv) the above "acyloxy" includes, for example, an acyl represented by the formula: $-(C=O)-R^3$, $-(C=O)-OR^3$, $-(C=O)-NR^3R^4$, $-(C=S)-NHR^3$, $-SO_2-R^{3a}$ or $-SO-R^{3a}$ wherein R^3 represents hydrogen, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, R^{3a} represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, R^4 represents hydrogen or C_{1-6} alkyl, or R^3 and R^4 may, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring.

The "hydrocarbon group" of the "hydrocarbon group which may be substituted" for R^3 or R^{3a} means a group formed by removing an optional hydrogen atom from a hydrocarbon compound, as exemplified by acyclic or cyclic hydrocarbon group such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl and aralkyl. Among them, the following C_{1-16} acyclic or cyclic hydrocarbon group is preferable:

a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.),

b) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.),

c) C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl, etc.),

d) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), and the C_{3-6} cycloalkyl being optionally condensed with one benzene ring,

e) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc.), preferably phenyl,

f) C_{7-19} aralkyl (e.g., benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably benzyl.

Among others, C_{1-6} alkyl, C_{6-14} aryl and C_{7-19} aralkyl are preferable.

Examples of the "substituent" for the "hydrocarbon group which may be substituted" include halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, ethylmethylamino, etc.),

acyl, acylamino, acyloxy, 5- to 7-membered saturated cyclic amino, sulfo, aromatic group which may be substituted, and so forth.

The "hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the hydrocarbon group and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

The above-mentioned "aromatic group which may be substituted" includes "aromatic group which may be substituted" for Ar' described hereinafter.

The "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "5- to 7-membered saturated cyclic amino", "acyl", "acylamino" and "acyloxy" mentioned above include, for example, those described in detail in the foregoing referring to the "substituents" for the "hydrocarbon group which may be substituted".

Of these, preferred "acyl" for "acyl", "acylamino" and "acyloxy" mentioned above is a group of the formula: $-(C=O)-R^3$, $-(C=O)-OR^3$, $-(C=O)-NR^3R^4$, $-(C=S)-NHR^3$, $-SO_2-R^{3a}$ or $-SO-R^{3a}$ where R^3 is (i) hydrogen,
(ii) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and sulfo, or
(iii) a heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally

halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and C_{6-10} aryloxy; and

R^{3a} is (i) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and sulfo, or

(ii) a heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and C_{6-10} aryloxy.

The "heterocyclic group" of the "heterocyclic group which may be substituted" for R^3 or R^{3a} includes, for example, a monovalent group formed by removing an optional hydrogen atom from a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic ring containing 1 to 4 hetero atoms of 1 or 2 species selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, preferably, (i) a 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic ring, (ii) a 5- to 10-membered non-aromatic heterocyclic ring or (iii) a 7- to 10-membered bridged heterocyclic ring.

The above-mentioned "5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic ring" includes, for example, an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole,

benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, phenoxathiine, pyrrole, imidazole, pyrazole, oxadiazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine, phthalimide, etc.; and a ring as formed through condensation of those rings, preferably a monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The above-mentioned "5- to 10-membered non-aromatic heterocyclic ring" includes, for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, etc.

The above-mentioned "7- to 10-membered bridged heterocyclic ring" includes, for example, quinuclidine, 7-azabicyclo[2,2,1]heptane, etc.

Preferable examples of the "heterocyclic group" include, for example, a 5- to 10-membered (monocyclic or bicyclic) heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely mentioned are an aromatic heterocyclic group such as 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2-, 3-, 4-, 5- or 8-quinolyl, 4-isoquinolyl, pyrazinyl, 2- or 4-pyrimidinyl, 3-pyrrolyl, 2-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1-indolyl, 2-indolyl, 2-isoindolylnyl, etc; and a non-aromatic heterocyclic group such as 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholino, etc.

Among these groups, a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely mentioned are 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholino, etc.

The "heterocyclic group which may be substituted" may have 1 to 5, preferably 1 to 3 substituents which the "aromatic ring assembly group which may be substituted" mentioned above may have. When the number of substituents is two or more, those substituents may be the same as or different from one another.

In the case that the "substituent" for the above "heterocyclic group which may be substituted" is "acyl", "acylamino" or "acyloxy", preferred "acyl" for these "acyl", "acylamino" or "acyloxy" is a group of the formula: $-(C=O)-R^3$, $-(C=O)-OR^3$, $-(C=O)-NR^3R^4$, $-(C=S)-NHR^3$, $-SO_2-R^{3a}$ or $-SO-R^{3a}$ where R^3 is (i) hydrogen,
(ii) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and sulfo, or
(iii) a heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6}

alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and C_{6-10} aryloxy; and

R^{3a} is (i) a hydrocarbon group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and sulfo, or

(ii) a heterocyclic group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and C_{6-10} aryloxy.

The "C_{1-6} alkyl" for R^4 includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "nitrogen-containing heterocyclic ring" formed by, taken together with the adjacent nitrogen atom, R^3 and R^4 includes, for example, a 5- to 7-membered nitrogen-containing heterocyclic ring having one nitrogen atom and optionally having 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Such examples include piperidine, morpholine, thiomorpholine, piperazine, pyrrolidine, etc.

Preferably, the above "acyl" is, for example, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-10} aryl-carbonyl (e.g.,

benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{6-10} aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered heterocycle carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, piperidinocarbonyl, 1-pyrrolidinylcarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), 5- or 6-membered heterocycle carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), C_{6-10} arylsulfonyl (e.g., benzenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl, etc.), etc.

The above-mentioned "acylamino" includes, for example, an amino substituted by 1 or 2 "acyl" described in detail in the foregoing referring to the "substituents" for the "aromatic ring assembly group which may be substituted". Preferred is an acylamino of the formula: $-NR^5COR^6$, $-NR^5COOR^{6a}$ or $-NR^5SO_2R^{6a}$ wherein R^5 represents hydrogen or C_{1-6} alkyl, R^6 represents hydrogen, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, and R^{6a} represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

The "C_{1-6} alkyl" for R^5 includes the "C_{1-6} alkyl" shown by R^4 above.

The "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted"

for R^6 or R^{6a} include the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" shown by R^3, respectively.

Preferred examples of the "acylamino" are formylamino, C_{1-6} alkyl-carboxamido (e.g., acetamido, etc.), C_{6-10} aryl-carboxamido (e.g., phenylcarboxamido, naphthylcarboxamido, etc.), C_{1-6} alkoxy-carboxamido (e.g., methoxycarboxamido, ethoxycarboxamido, propoxycarboxamido, butoxycarboxamido, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), etc.

The above-mentioned "acyloxy" includes, for example, an oxy substituted by one "acyl" described in detail in the foregoing referring to the "substituents" for the "aromatic ring assembly group which may be substituted". Preferred is an acyloxy of the formula: $-O-COR^7$, $-O-COOR^7$ or $-O-CONHR^7$ wherein R^7 represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

The "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^7 include the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" shown by R^3, respectively.

Preferred examples of the "acyloxy" are C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propanoyloxy, etc.), C_{6-10} aryl-carbonyloxy (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-10} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, etc.

The "substituent" for the "aromatic ring assembly

group which may be substituted" for Ar preferably includes halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and formyl.

The "fused aromatic group" of the "fused aromatic group which may be substituted" for Ar is meant to indicate a monovalent group by removing an optional hydrogen atom from a fused polycyclic (preferably bi-cyclic to tetra-cyclic, more preferably bi-cyclic or tri-cyclic) aromatic ring. The "fused polycyclic aromatic ring" includes a fused polycyclic aromatic hydrocarbon group, a fused polycyclic aromatic heterocyclic ring, etc.

The "fused polycyclic aromatic hydrocarbon group" includes, for example, a fused polycyclic (preferably bi-cyclic or tri-cyclic) C_{10-14} aromatic hydrocarbon group (e.g., naphthalene, indene, anthracene, etc.).

The "fused polycyclic aromatic heterocyclic ring" includes, for example, a 9- to 14-membered, preferably 9- or 10-membered fused polycyclic aromatic heterocyclic ring containing one or more (e.g., 1 to 4) hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely mentioned is an aromatic heterocyclic ring such as benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiazine, phenoxazine, phthalimide, etc.

As specific examples of the "fused aromatic group", mentioned are 1-naphthyl, 2-naphthyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 2-benzofuranyl, 2-benzothiazolyl, 2-benzimidazolyl, 1-indolyl, 2-indolyl, 3-indolyl, etc. Preferred are 1-naphthyl and 2-naphthyl, etc.

For the "substituents" for the "fused aromatic group which may be substituted" and their number, referred to are the same as those mentioned above for the "aromatic ring assembly group which may be substituted" for Ar.

Ar is preferably an aromatic ring assembly group which may be substituted. Among others, the aromatic ring assembly group is preferably composed of two or three aromatic rings selected from the group consisting of benzene, thiophene, pyridine, pyrimidine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, naphthalene and benzofuran. More preferred is 2-, 3- or 4-biphenylyl.

Preferred examples of Ar are aromatic ring assembly groups which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy. More preferred is a 2-, 3- or 4-biphenylyl (but even more preferably, 4-biphenylyl) which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms,

C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated-C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy.

The "aromatic group" of the "aromatic group which may be substituted" for Ar' includes, for example, a monocyclic aromatic group, an aromatic ring assembly group, a fused aromatic group, etc. The "aromatic ring assembly group" and the "fused aromatic groups" are the same as those mentioned in detail hereinabove for the "aromatic ring assembly group" and the "fused aromatic groups" for Ar.

The "monocyclic aromatic group" includes, for example, a monovalent group by removing an optional hydrogen atom from a benzene ring or a 5- or 6-membered aromatic heterocyclic ring.

The "5- or 6-membered aromatic heterocyclic ring" includes, for example, a 5- or 6-membered aromatic heterocyclic ring containing one or more (e.g., 1 to 3) hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely mentioned are thiophene, furan,

pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, etc.

Specific examples of the "monocyclic aromatic group" are phenyl, 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2- or 4-imidazolyl, 3- or 4-pyrazolyl, 2-, 3- or 4-pyridyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, etc.

The "substituents" for the "aromatic group which may be substituted" and their number are the same as those mentioned above for the "aromatic ring assembly group which may be substituted" for Ar.

Ar' is preferably an aromatic ring assembly group which may be substituted, or a fused aromatic group which may be substituted. More preferred is an aromatic ring assembly group which may be substituted.

The "C_{1-6} alkylene" of the "C_{1-6} alkylene which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl" for X includes, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, etc.

The "C_{2-6} alkenylene" of the "C_{2-6} alkenylene which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl" for X includes, for example, $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH=CH-$, etc.

The "C_{2-6} alkynylene" of the "C_{2-6} alkynylene which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl" for X includes, for example, $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.

The above oxo and C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) may be substituted at the substitutable positions. When the number of the

substituents is two or more, those substituents may be the same as or different from one another.

The "hydrocarbon group which may be substituted" and the "acyl" for R^8 are the same as those mentioned in detail above. R^8 is preferably hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, etc.

X is preferably a C_{1-6} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, etc.); a group of the formula: $-(CH_2)p-X^1-$ or $-SO_2-NR^8-$ wherein each symbol is as defined above; etc. Of those, more preferably, X^1 is O or NR^8 (more preferably O); and R^8 is hydrogen or a C_{1-3} alkyl-carbonyl (e.g., acetyl, etc.).

X is preferably a divalent C_{1-6} aliphatic hydrocarbon group (e.g., C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, etc.) which may contain an oxygen atom, more preferably a C_{1-3} alkylene, $-CH_2-O-$, etc.

The "divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom" of the "divalent C_{1-6} aliphatic hydrocarbon group which may have an oxygen atom or a sulfur atom and may be substituted" for Y includes, for example, a saturated or unsaturated divalent C_{1-6} aliphatic hydrocarbon group which may contain one or two, preferably one oxygen or sulfur atom at any position between carbon atoms or at the terminal. Concretely mentioned are a C_{1-6} alkylene, a C_{2-6} alkenylene, a C_{2-6} alkynylene, a group of the formula: $-(CH_2)m-Y^1-(CH_2)n-$ wherein $-Y^1-$ represents -O-, -S-, -SO- or $-SO_2-$; m represents an integer of 0 to 4; n represents an integer of 1 to 5; and m+n is an integer of 1 to 5, etc. Preferred is a divalent C_{1-6} aliphatic hydrocarbon group.

The above "C_{1-6} alkylene", "C_{2-6} alkenylene" and "C_{2-6} alkynylene" are the same as those mentioned in detail above for the "C_{1-6} alkylene", "C_{2-6} alkenylene" and "C_{2-6} alkynylene" for X.

The "substituent" for the "divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), etc. One to three such substituents may be substituted at the substitutable positions of the divalent C_{1-6} aliphatic hydrocarbon group. When the number of the substituents is two or more, those substituents may be the same as or different from one another.

Y is preferably a divalent C_{1-6} aliphatic hydrocarbon group, more preferably a C_{1-6} alkylene.

The "lower alkyl" of the "lower alkyl which may be substituted" for R^1 or R^2 includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), etc. Preferred is methyl, ethyl and propyl.

The "lower alkyl group which may be substituted" may have 1 to 5, preferably 1 to 3 substituents, such as (1) those which the "aromatic ring assembly group which may be substituted" may have or (2) C_{6-10} aryl. When the number of the substituents is two or more, those substituents may be the same as or different from one another.

The "nitrogen-containing heterocyclic ring" of the "nitrogen-containing heterocyclic ring which may be substituted" to be formed by R^1 and R^2 along with the adjacent nitrogen atom includes, for example, a 3- to 8-membered nitrogen-containing heterocyclic ring having one nitrogen atom and optionally having 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely mentioned are aziridine, azetidine, morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine, hexamethyleneimine, heptamethyleneimine,

as well as unsaturated cyclic amines corresponding to those rings (e.g., 1,2,5,6-tetrahydropyridine, etc.), etc. Of those, preferred are morpholine, piperidine, piperazine, pyrrolidine, etc.

The "nitrogen-containing heterocyclic ring which may be substituted" may have 1 to 3 substituents selected from the group consisting of (1) "substituents" for the "hydrocarbon group which may be substituted", (2) oxo and (3) C_{7-19} aralkyl. Preferred examples of the substituents are C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, etc.), hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 7-membered cyclic amino (e.g., morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, hexamethylenimin-1-yl, etc.), C_{1-6} alkyl-carboxamido (e.g., acetamido, etc.), C_{1-6} alkoxy-carboxamido (e.g., methoxycarboxamido, ethoxycarboxamido, etc.), aromatic group which may be substituted (e.g., a C_{6-10} aryl (preferably, phenyl or 1- or 2-naphthyl) or 5- or 6-membered aromatic heterocyclic group (preferably, 2-, 3- or 4-pyridyl), each of which group may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, cyano, C_{1-6} alkyl and C_{1-6} alkoxy, etc.), oxo, etc.

R^1 and R^2 each is preferably C_{1-6} alkyl.

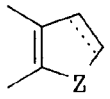
The "group of the formula: -X-Ar" is substituted at the substitutable position of Ring A. The "substituent" for the "benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above" for Ring A includes, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), optionally

halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, hydroxy, amino, etc. The "optionally halogenated C_{1-6} alkyl" and the "optionally halogenated C_{1-6} alkoxy" are the same as those mentioned in detail above for the "optionally halogenated C_{1-6} alkyl" and the "optionally halogenated C_{1-6} alkoxy" for Ar.

One to three such substituents may be substituted at the substitutable positions of Ring A. When the number of the substituents is two or more, those substituents may be the same as or different from one another.

Ring A is preferable a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol is as defined above.

The "group of the formula: $-Y-NR^1R^2$" is substituted at the substitutable position of Ring B. The "4- to 8-membered ring" of the "4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above" for Ring B may have one double bond apart from the part at which Ring B is condensed with Ring A, and includes a 4- to 8-membered carbocyclic or heterocyclic ring which may contain 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Specific examples of those rings, mentioned is a ring of the formula:



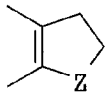
wherein ----- represents a single bond or a double bond; and Z represents (i) a bond, (ii) a C_{1-4} alkylene, (iii) a C_{2-4} alkenylene, (iv) $-O-CH_2-$, (v) $-O-CH_2-CH_2-$ or (vi) a group of the formula: $-NR^{8a}-CH_2-$ or $-NR^{8a}-CH_2-CH_2-$ wherein R^{8a} has the same meaning as R^8.

R^{8a} is preferably hydrogen, optionally halogenated

C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, etc. More preferred is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-3} alkylsulfonyl, etc.

Z is preferably C_{1-3} alkylene, $-NR^{8a}-CH_2-$, etc. More preferably, it is ethylene.

The "4- to 8-membered ring" is preferably a 4- to 8-membered ring of the formula:

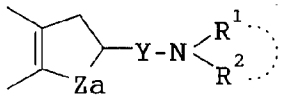


wherein Z has the same meanings as above. More preferred is a 6-membered carbocyclic or heterocyclic ring which does not have any double bond apart from the part at which it is condensed with Ring A, and which may have one oxygen atom or imino in addition to carbon atoms.

The "substituent" for the "4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above" includes, for example, oxo, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), etc. One to three such substituents may be substituted at the substitutable positions of the ring. When the number of the substituents is two or more, those substituents may be the same as or different from one another.

Ring B is preferably a 6-membered carbocyclic or heterocyclic ring substituted by the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above. More preferably Ring B is a ring of the

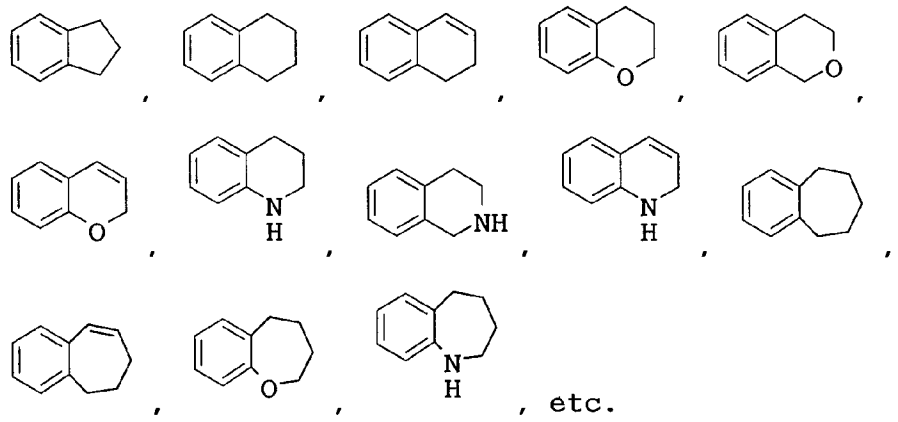
formula:



wherein Za represents C_{1-3} alkylene or a group of the formula:

$-NR^{8c}-CH_2-$ wherein R^{8c} is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl; and the other symbols have the same meanings as above. Of those, Za is preferably ethylene.

The fused ring to be formed by Ring A and Ring B is preferably a ring of the formula:



, etc.

In compounds (I) and (I'), preferred is a compound wherein Ar and Ar' each is an aromatic ring assembly group (preferably 2-, 3- or 4-biphenylyl) which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6}

alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido;

X is C_{1-3} alkylene which may contain an oxygen atom;

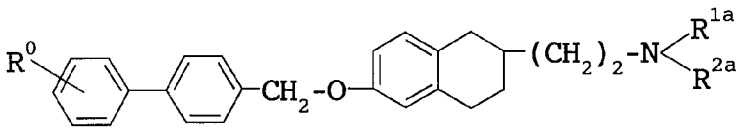
Y is C_{1-6} alkylene;

R^1 and R^2 each is C_{1-6} alkyl;

Ring A is a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B is a 6-membered carbocyclic or heterocyclic ring substituted by the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above.

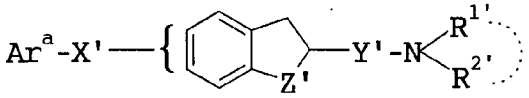
More preferred is a compound of the formula:



wherein R^0 is 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido; and

R^{1a} and R^{2a} each is C_{1-6} alkyl.

Also preferred is a compound of the formula:



wherein Ar^a is (i) 2, 3- or 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, amino, formyl and C_{1-6} alkyl-carboxamido, (ii) 4-(2-thienyl)phenyl or 4-(3-

thienyl)phenyl, (iii) 4-(3-pyridyl)phenyl, (iv) 6-phenyl-3-pyridyl which may be substituted by a C_{1-6} alkoxy, (v) 5-phenyl-1,3,4-oxadiazol-2-yl, (vi) 4-(2-naphthyl)phenyl, (vii) 4-(2-benzofuranyl)phenyl, (viii) 1- or 2-naphthyl, (ix) 2-quinolyl, (x) 2-benzothiazolyl or (xi) 2-benzofuranyl;

X' is $-CH_2-O-$, $-SO_2-NH-$ or a group of the formula: $-CH_2-NR^{8'}-$ wherein $R^{8'}$ is hydrogen or C_{1-3} alkyl-carbonyl;

Y' is C_{1-6} alkylene;

Z' is $-CH_2-CH_2-$ or a group of the formula: $-NR^{8''}-CH_2-$ wherein $R^{8''}$ is hydrogen, C_{1-3} alkyl, C_{1-3} alkyl-carbonyl or C_{1-3} alkylsulfonyl; and

$R^{1'}$ and $R^{2'}$ each is C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of di-C_{1-3} alkylamino, C_{1-3} alkoxy-carbonyl and phenyl, or

$R^{1'}$ and $R^{2'}$ form, taken together with the adjacent nitrogen atom, a pyrrolidin-1-yl, piperidino or piperazin-1-yl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, C_{1-3} alkoxy-carbonyl, piperidino, phenyl and benzyl.

Especially preferred are 6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
6-(4-biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin,
2-(N,N-dimethylamino)methyl-6-(4'-methoxybiphenyl-4-yl)methoxytetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methylbiphenyl-4-yl)methoxytetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methoxybiphenyl-4-yl)methoxytetralin,

(+)-6-(2',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-[4-(1,3-benzodioxol-5-yl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-(3',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin and salts thereof.

As the salts of compound (I) and compound (I'), for example, inorganic salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids can be mentioned. Preferable examples of inorganic salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salts, magnesium salts and barium salts; aluminum salts, etc. Preferred salts with organic bases are exemplified by salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred salts with inorganic acids are exemplified by salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Preferred salts with organic acids are exemplified by salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Preferred salts with basic amino acids are exemplified by salts with arginine, lysine, ornithine, etc. Preferred salts with acidic amino acids are exemplified by salts with aspartic acid, glutamic acid, etc.

Among others, pharmaceutically acceptable salts are preferable. Preferable examples include, for example, when compound (I) or (i') has a acidic functional group, alkali metal salts (e.g., sodium salt,

potassium salt, etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt, etc.), and ammonium salts; and when compound (I) or (I') has a basic functional group, inorganic salts such as hydrochloride, sulfate, phosphate and hydrobromide, or, organic salts such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate and tartrate.

Process for producing compound (I) is mentioned below.

Compound (I) can be produced by any *per se* known means, for example, by the following processes 1 to 4, etc. Compound (I') can be produced in accordance with the production of compound (I).

Compounds described in the following processes 1 to 4 include their salts. For their salts, for example, referred to are the same as the salts of compound (I).

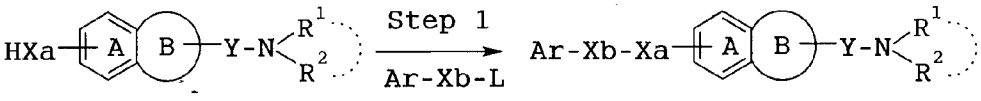
"Room temperature" is meant to indicate a temperature falling between 0° C and 30° C.

For example, compound (I) wherein X contains an oxygen atom, a sulfur atom which may be oxidized (S, SO or SO_2) or a group of the formula: NR^{8a} wherein R^{8a} has the same meanings as above, is produced according to the methods mentioned below. Other compound (I) wherein X contains none of an oxygen atom, a sulfur atom which may be oxidized and a group of the formula: NR^{8a} wherein R^{8a} has the same meanings as above, can also be produced in the same manner.

Unless otherwise specifically indicated, the symbols in the chemical structures in the schemes mentioned below have the same meanings as above.

Process 1

Scheme 1



(II) (Ia)

In those formulae, Xa represents an oxygen atom, a sulfur atom which may be oxidized or a group of the formula: NR^{8a} wherein R^{8a} has the same meanings as above.

(Step 1)

Compound (II) is subjected to alkylation or acylation to obtain compound (Ia).

The "alkylation" and "acylation" may be effected in any *per se* known manner, for example, according to the methods described in Organic Functional Group Preparations, 2nd Ed., Academic Press Inc., 1989.

Concretely, compound (II) is reacted with a compound of the formula: Ar-Xb-L wherein Xb represents a group formed by removing Xa from X, and L represents a leaving group or a hydroxy, to obtain compound (Ia).

The "leaving group" for L includes, for example, halogen atoms (e.g., chloro, bromo, iodo, etc.), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), C_{6-10} arylsulfonyloxy which may be substituted, etc. The "substituent" for the "C_{6-10} arylsulfonyloxy which may be substituted" includes, for example, 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy. Specific examples of the "C_{6-10} arylsulfonyloxy which may be substituted" are benzenesulfonyloxy, p-toluenesulfonyloxy, 1-naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy, etc.

Compound (II) can be produced in any *per se* known manner, for example, according to the methods of the following schemes 2 to 4 or analogous methods thereto.

In the case that L is a leaving group, for example, compound (II) is reacted with an equivalent amount or an excessive amount of a compound of the formula: Ar-Xb-L wherein each symbol is as defined above, in an inert solvent. If desired, a base is added to the reaction system. Where Xa is a group of the formula: NR^{8a} wherein R^{8a} has the same meanings as above, the addition of the base is not always indispensable.

The reaction temperature falls between -20°C and 100°C, preferably between room temperature (0°C to 30°C) and 80°C. The reaction time falls between 0.5 hours and 1 day.

The inert solvent includes, for example, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used either singly or as a suitable mixture of two or more species. Of those, preferred are acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, pyridine, etc.

The "base" includes, for example;

(1) strong bases such as alkali metal or alkaline earth metal hydrides (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), alkali metal or alkaline earth metal amides (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethylsilazide, sodium hexamethylsilazide, potassium hexamethylsilazide, etc.), alkali metal or alkaline earth metal lower-alkoxides (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), etc.;

(2) inorganic bases such as alkali metal or alkaline earth metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, barium

hydroxide, etc.), alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate, etc.), alkali metal or alkaline earth metal hydrogencarbonates (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), etc.; or

(3) organic bases such as amines e.g., triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), etc., basic heterocyclic compounds, e.g., pyridine, imidazole, 2,6-lutidine, etc.

Preferably, the alkylation is effected by stirring compound (II) with 1 to 2 equivalents of a compound of the formula: Ar-Xb-L wherein each symbol is as defined above, and 1 to 5 equivalents of a base (e.g., potassium carbonate, sodium hydride, sodium hydroxide, etc.), in acetonitrile or DMF, for 1 to 20 hours. The preferred reaction temperature varies, depending on the base used. For example, when sodium hydride is used, the reaction temperature is preferably room temperature; and when potassium carbonate is used, the preferred reaction temperature falls between room temperature and 80° C.

The acylation is preferably effected by stirring compound (II) with 1 to 1.5 equivalents of a compound of the formula: Ar-Xb-L wherein each symbol is as defined above, and 1 to 5 equivalents of a base (e.g., sodium hydride, sodium hydroxide, potassium carbonate, sodium hydrogencarbonate, triethylamine, etc.), in an inert solvent (e.g., single or mixed solvent of water, ethyl acetate, DMF, acetonitrile and/or pyridine), at room temperature for 1 to 6 hours.

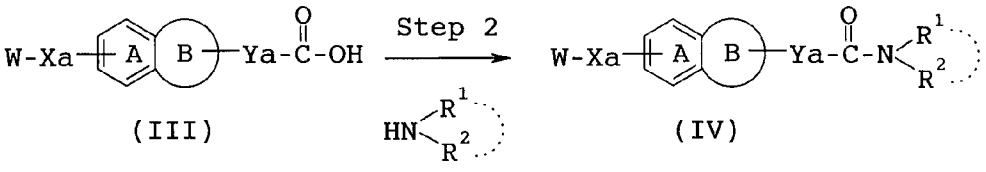
In the case that L is a hydroxy group, compound (II) is subjected to Mitsunobu reaction.

The Mitsunobu reaction may be attained, for

example, by stirring compound (II) with 1 to 3 equivalents, preferably from 1.1 to 2 equivalents of a compound of the formula: Ar-Xb-L wherein each symbol is as defined above, in the presence of 1 to 2 equivalents of a triarylphosphine (e.g., triphenylphosphine, etc.) and 1 to 2 equivalents of DEAE (diethyl azodicarboxylate) in an inert solvent, for 1 to 24 hours.

The inert solvent includes, for example, ethers, etc. Preferred is tetrahydrofuran (THF).

Scheme 2



In those formulae, W represents a hydrogen atom or a protective group; and Ya represents a group formed by removing a methylene from Y.

For the "protective group" for W, referred to are the same as those for the "protective group for hydroxy group" which will be mentioned hereinafter. W is preferably a C_{1-6} alkyl or a benzyl which may be substituted.

(Step 2)

Compound (III) is subjected to amidation to obtain compound (IV).

Compound (III) is an easily-available known compound. Examples for the production of compound (II) are disclosed in JP-A-2-96552, JP-A-6-206851, J. Med. Chem., 1326 (1989), etc.

The production of some specific examples of compound (III) wherein Xa is an oxygen atom and W is a methyl, is disclosed in other references. For example, (1) methods for producing 1,2,3,4-tetrahydro-6-methoxynaphthalene-2-acetic acid are disclosed in Synthetic Communications 11, 803-809 (1981), etc.; and (2) methods for producing 1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylic acid and 1,2,3,4-tetrahydro-6-methoxynaphthalene-2-butyric acid are disclosed in J. Chem. Soc. Perkin Trans. I, 1889-1893 (1976), etc.

The production or some other examples of compound (III) wherein Xa is an imino and W is hydrogen, 6-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and its ethyl ester is disclosed in Zhur. Obschch. Khim., p. 1446 (1952), etc.

In other case that compound (III) which is 7-methoxy-2-oxo-1,2,3,4-tetrahydroquinoline-3-acetic acid or 8-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-1-benzazepine-3-carboxylic acid, it can be produced according to the methods described in J. Am. Chem. Soc., 77, 5932-5933 (1955) or analogous methods thereto. Compound (III) which is 7-methoxy-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid can be produced according to the methods described in JP-A-7-126267.

The "amidation" may be effected in any *per se* known methods, for example, (1) by reacting compound (III) with a compound of the formula: HNR^1R^2 in the presence of a dehydrating condensing agent, or (2) by reacting a reactive derivative of compound (III) with a

compound of the formula: HNR^1R^2.

In the above reaction (1), compound (III) is reacted with 1 to 5 equivalents of a compound of the formula: HNR^1R^2 in the presence of 1 to 2 equivalents of a dehydrating condensing agent, in an inert solvent, at room temperature, for 10 to 24 hours. If desired, 1 to 1.5 equivalents of 1-hydroxybenzotriazole (HOBT) and/or 1 to 5 equivalents of a base (e.g., triethylamine, etc.) may be added to the reaction system.

The "dehydrating condensing agent" includes, for example, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC), etc. Of those, preferred is WSC.

The inert solvent includes, for example, nitriles (preferably, acetonitrile), amides (preferably, DMF), halogenated hydrocarbons (preferably, dichloromethane), ethers (preferably, THF), etc., which may be used either singly or as a suitable mixture of two or more species.

In the above reaction (2), a reactive derivative of compound (III) is reacted with 1 to 5 equivalents, preferably 1 to 3 equivalents of a compound of the formula: HNR^1R^2, in an inert solvent, at -20 to 50°C, preferably at room temperature, for 5 minutes to 40 hours, preferably 1 to 18 hours. If desired, 1 to 10 equivalents, preferably 1 to 3 equivalents of a base may be in the reaction system.

The "reactive derivative" of compound (III) includes, for example, its acid halides (e.g., acid chlorides, acid bromides, etc.), mixed acid anhydrides (e.g., acid anhydrides with C_{1-6} alkyl-carboxylic acids, C_{6-10} aryl-carboxylic acids or C_{1-6} alkyl-carbonic acids, etc.), and active esters (e.g., esters with phenol which may be substituted, 1-hydroxybenzotriazole or N-hydroxysuccinimide, etc.). The "substituent" for the

"phenol which may be substituted" includes, for example, 1 to 5 substituents selected from the group consisting of halogen atoms, nitro, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy. Specific examples of the "phenol which may be substituted" are phenol, pentachlorophenol, pentafluorophenol, p-nitrophenyl, etc. The reactive derivatives are preferably acid halides.

The "base" is the same as those mentioned in detail hereinabove for the step 1. Preferred are potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc. The inert solvent includes, for example, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used either singly or as a suitable mixture of two or more species. Of those, preferred are acetonitrile, dichloromethane, chloroform, etc.

(Step 3)

Compound (IV) is subjected to reduction to obtain compound (V).

The reduction may be effected in any *per se* known manner, for example, according to the methods described in Organic Functional Group Preparations, 2nd Ed., Academic Press Inc., 1989, etc. Concretely, for example, (1) compound (IV) is reacted with a metal hydride; (2) compound (IV) is reacted with a metal; or (3) compound (IV) is subjected to catalytic reduction.

In the reaction (1), compound (IV) is reacted with 1 to 20 equivalents, preferably 1 to 6 equivalents of a metal hydride in an inert solvent.

The "metal hydride" includes, for example, aluminum hydride, lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium borohydride

cyanide, lithium borohydride cyanide, borane complexes (e.g., borane-THF complex, catechol-borane, etc.), dibutyl aluminum hydride, as well as mixtures of those metal hydrides and Lewis acids (e.g., aluminum chloride, titanium tetrachloride, cobalt chloride, etc.) or phosphorus oxychloride, etc. Preferred metal hydrides are lithium aluminum hydride and aluminum hydride.

The inert solvent includes, for example, ethers.

The reaction temperature varies, depending on the metal hydride used, but generally falls between -70 and 100°C. Where lithium aluminum hydride is used, the reaction temperature may be between room temperature and 80°C. Where borane complex is used, the reaction temperature may be between room temperature and 100°C, preferably between room temperature and 60°C.

The reaction time falls between 1 and 48 hours.

In the reaction (2), compound (IV) is reacted with 1 to 20 equivalents, preferably 2 to 6 equivalents of a metal in an inert solvent.

The "metal" includes, for example, zinc, iron, sodium, potassium, etc.

The inert solvent includes, for example, organic acids (e.g., acetic acid, propionic acid, methanesulfonic acid, etc.), ethers, aromatic solvents, hydrocarbons, etc., which may be used either singly or as a suitable mixture of two or more species. Preferred are ethers.

The reaction temperature varies, depending on the metal used, but generally falls between -70 and 100°C. Where zinc is used, the reaction temperature may fall between room temperature and 80°C.

The reaction time falls between 1 and 10 hours.

In the reaction (3), compound (IV) is reacted with a catalytic amount to 10 equivalents of a metal catalyst (e.g., Raney nickel, etc.) and a phosphorus sulfide compound (e.g., phosphorus pentasulfide,

phosphorus trisulfide, etc.), in an inert solvent (e.g., alcohols, etc.), at room temperature to 100° C under a hydrogen pressure of 1 to 100 atmospheres, for 1 to 48 hours.

In the above step 3, by selecting the reaction condition for the reduction, a carbonyl group and a lactam which are functional groups in the molecule (IV), are reduced to give a hydroxy and a cyclic amino, respectively.

In the case that the fused ring formed by Ring A and Ring B is, for example, 2-oxo-1,2,3,4-tetrahydroquinoline or 2-oxo-2,3,4,5-tetrahydro-1H-1-benzazepine, 1,2,3,4-tetrahydroquinoline and 2,3,4,5-tetrahydro-1H-1-benzazepine are obtained, respectively by using the above borane complexes. Concretely, compound (IV) is reacted with one equivalent to an excessive amount, preferably 1 to 5 equivalents of borane complexes in an ethers, at room temperature to 100° C, preferably at room temperature to 60° C, for 0.1 to 48 hours, preferably 1 to 5 hours.

(Step 4)

Compound (V) is subjected to deprotection to obtain compound (IIa).

Briefly, compound (V) wherein W is a protective group is subjected to deprotection in *per se* known manner.

The deprotection may be effected, for example, according to the methods described in Organic Functional Group Preparations mentioned above, etc. Concretely, the deprotection includes, for example, deprotection by acid, catalytic reduction, hydrolysis, nucleophilic substitution, etc., which may be suitably selected in accordance with the protective group W.

In the case that W is C_{1-6} alkyl, preferably methyl, for example, compound (V) is reacted with 1 to 100

equivalents of an acid in the absence or presence of an insert solvent, at -78 to 200°C, for 5 minutes to 24 hours.

The acid includes, for example, mineral acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, etc.), Lewis acids (e.g., aluminum chloride, boron tribromide, etc.), and halogenated silane reagents (e.g., iodotrimethylsilane, bromotrimethylsilane, etc.).

The inert solvent includes, for example, water, halogenated hydrocarbons, acetic acid, etc., which may be used either singly or as a suitable mixture of two or more species.

Preferably, compound (V) is reacted with 5 to 100 equivalents of hydrobromic acid in water or acetic acid, at 100 to 130°C, for 1 to 5 hours.

In the case that W is a benzyl which may be substituted, for example, compound (V) is subjected to catalytic reduction in general.

Briefly, compound (V) is reacted with a catalytic amount of a metal catalyst (e.g., Raney nickel, platinum hydroxide, palladium metal, palladium-carbon, etc.), in an inert solvent (e.g., alcohols, etc.), at room temperature to 100°C, under a hydrogen pressure of 1 to 100 atmospheres, for 1 to 48 hours. Preferably, compound (V) is reacted with a catalytic amount of palladium-carbon, in alcohols (e.g., ethanol, etc.), under a hydrogen pressure of 1 to 10 atmospheres, at room temperature to 50°C, for 1 to 10 hours.

In the case that W is C_{1-6} alkyl-carbonyl, a benzoyl or a C_{7-10} aralkyl-carbonyl, for example, compound (V) is subjected to hydrolysis.

Briefly, compound (V) is reacted with 2 to 100 equivalents, preferably 5 to 10 equivalents of an alkali in an inert solvent, at room temperature to 120°C, preferably at room temperature to 60°C, for 5

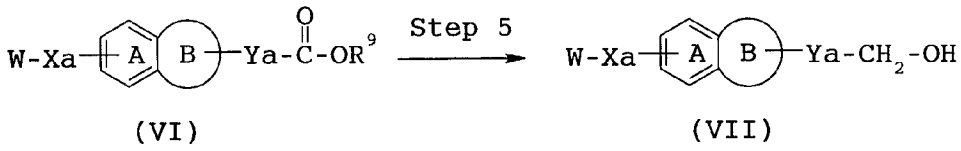
minutes to 100 hours, preferably for 1 to 20 hours.

The alkali includes, for example, hydroxides of inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, etc. Of those, preferred is sodium hydroxide.

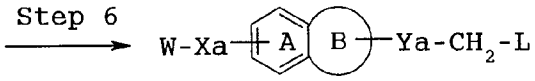
The inert solvent includes, for example, water, alcohols, ethers, etc., which may be used either singly or as a suitable mixture of two or more species. Of those, preferred is a mixed solvent of water-methanol.

Preferably, the solvent is a mixed solvent of water-methanol, the reaction temperature falls between room temperature and 60°C, and the reaction time falls between 5 and 10 hours.

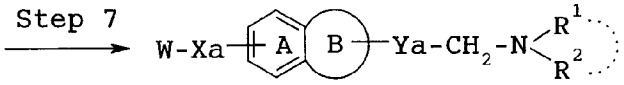
Scheme 3



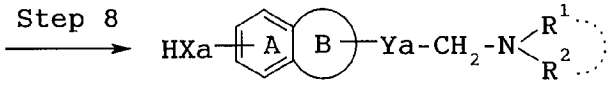
(VI) (VII)



(VIII)



(IX)



(IIa)

In those formulae, R^9 represents a protective group for carboxy; and L represents a leaving group.

The "protective group for carboxy" for R^9 are the

same as those for the "protective group for carboxy" which will be mentioned hereinafter. R^9 is preferably a C_{1-6} alkyl.

The "leaving group" for L are the same as those mentioned above for L.

(Step 5)

Compound (VI) is subjected to reduction to obtain compound (VII).

Compound (VI) is easily available, and can be obtained, for example, by subjecting compound (III) to esterification in *per se* known manner.

The reduction may be effected in any *per se* known manner, for example, according to the methods described in Organic Functional Group Preparations mentioned above, etc. For the reaction condition for the reduction, referred to is the same as that for the step 3. Preferably employed are metal hydrides.

Concretely, for example, compound (VI) is reacted with 1 to 20 equivalents, preferably 1 to 6 equivalents of a metal hydride (preferably, lithium aluminum hydride) in an inert solvent.

The inert solvent includes, for example, ethers, alcohols, aromatic solvents, etc., which may be used either singly or as a suitable mixture of two or more species.

The reaction temperature varies, depending on the metal hydride used, but, in general, falls between -70 and 100°C. Where lithium aluminum hydride is used, the reaction temperature is preferably between room temperature and 50°C.

(Step 6)

A leaving group is introduced into compound (VII) to obtain compound (VIII).

In the case that L is a halogen in compound (VIII),

compound (VII) is reacted with a halogenating reagent.

For example, where a commercially-available halogenating reagent (e.g., hydrobromic acid, phosphorus tribromide, phosphorus pentabromide, thionyl chloride, etc.) is used as a halogenating reagent, the halogenation may be effected in any *per se* known manner. For example, where hydrobromic acid is used as a halogenating reagent, compound (VII) may be reacted with 1.5 to 5 equivalents of the hydrobromic acid at 80 to 130°C for 1 to 18 hours.

Where the halogenating reagent is prepared, 1 to 1.5 equivalents of bromine or iodine is mixed with the same amount of triphenylphosphine in an inert solvent (e.g., nitriles, ethers, etc.) at room temperature to give a halogenating reagent. The thus-prepared halogenating reagent is reacted with compound (VII) in the same solvent at room temperature for 0.5 to 18 hours, preferably from 0.5 to 3 hours.

In the case that L is a sulfonyloxy (e.g., methanesulfonyloxy, p-toluenesulfonyloxy, benzenesulfonyloxy, etc.) in compound (VIII), compound (VII) is stirred with one equivalent or an excessive amount, preferably 1 to 1.5 equivalents of a sulfonating reagent (e.g., methanesulfonyl chloride, p-toluenesulfonyl chloride, benzenesulfonyl chloride, etc.) along with a base in an inert solvent at -50 to 50°C, preferably at room temperature, for 1 to 24 hours.

The "base" is the same as those mentioned in detail above for the step 1. Especially preferred are amines such as triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, etc.; and basic heterocyclic compounds such as pyridine, imidazole, 2,6-lutidine, etc. The amount of the base to be used is 1 to 8 equivalents relative to the sulfonating reagent used.

The inert solvent includes, for example,

halogenated hydrocarbons, nitriles, esters, etc., which may be used either singly or as a suitable mixture of two or more species.

The sulfonyloxy group in the resultant compound (VIII) may be subjected to iodation. For this, for example, compound (VIII) is reacted with 1 to 10 equivalents, preferably 1 to 3 equivalents of sodium iodide or potassium iodide in an inert solvent (e.g., ketones, ethers, etc.) at room temperature to 100°C, preferably at 30 to 60°C, for 1 to 24 hours.

(Step 7)

Compound (VIII) is subjected to amination to obtain compound (IX).

The amination may be effected in any *per se* known method, for example, according to the methods described in Organic Functional Group Preparations mentioned above, etc. Concretely, for example, compound (VIII) is stirred with 1 to 5 equivalents, preferably 1 to 2 equivalents of a compound of the formula: HNR^1R^2 in an inert solvent at room temperature to 100°C, preferably at room temperature to 50°C, for 0.5 hours to one day. In general, 1 to 5 equivalents, preferably 1 to 3 equivalents of a base is added to the reaction system.

The "base" is the same as those mentioned in detail hereinabove for the step 1. Especially preferred are tertiary amines such as triethylamine, etc.; and alkali metal or alkaline earth metal carbonates, etc.

The inert solvent includes, for example, water, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, etc., which may be used either singly or as a suitable mixture of two or more species. Of those, preferred are acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, etc.

Preferably, compound (VIII) is stirred with 1 to 2

equivalents of a compound of the formula: HNR^1R^2, along with 1 to 3 equivalents of a base (e.g., potassium carbonate, triethylamine, etc.) in an inert solvent (e.g., acetonitrile, DMF, etc.), at room temperature to 50°C, for 10 hours to one day.

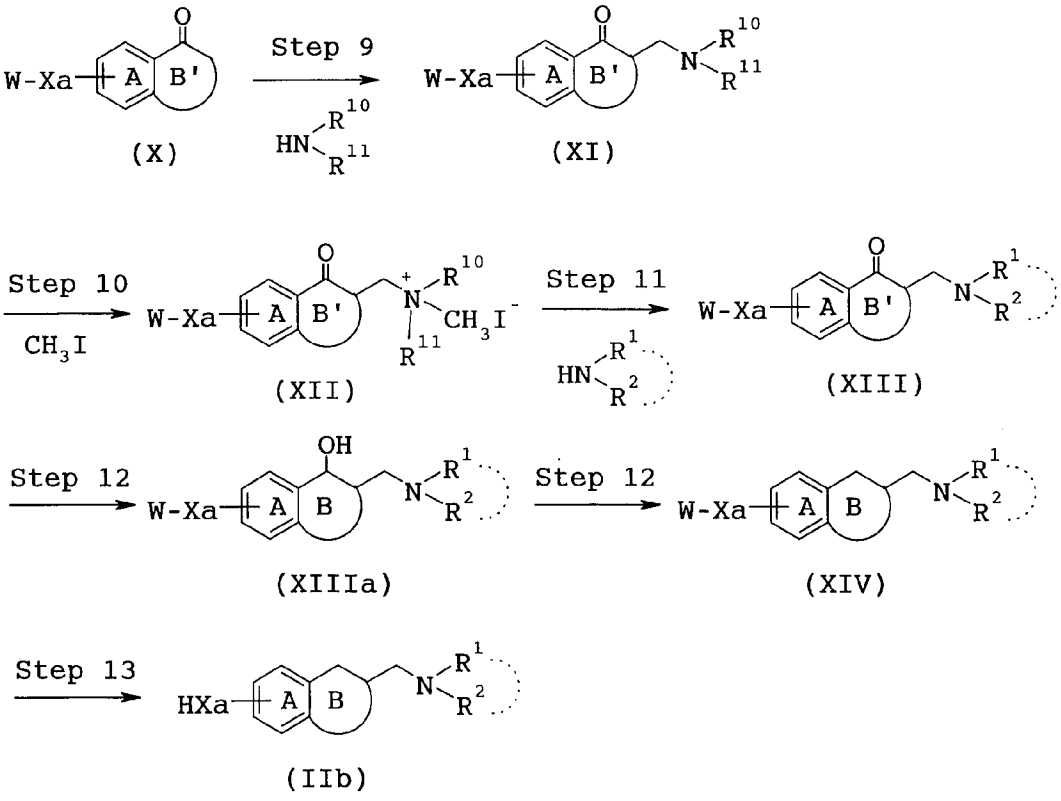
(Step 8)

Compound (IX) is subjected to deprotection to obtain compound (IIa).

The deprotection may be effected under the same reaction condition as that for the step 4.

Compound (II) wherein Y is a methylene may be obtained according to the following scheme 4.

Scheme 4



In those formulae, Ring B' corresponds to Ring B

having an oxo; and R^{10} and R^{11} each represents a C_{1-6} alkyl or a benzyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and nitro.

(Step 9)

Compound (X) is subjected to Mannich reaction to obtain compound (XI).

Compound (X) is easily available, and can be produced by any *per se* known methods.

The Mannich reaction may be effected in any *per se* known manner, for example, according to the methods described in WO 92/05143, etc. Concretely, for example, compound (X) is reacted with an excessive amount of formaldehyde or paraformaldehyde and 1 to 5 equivalents, preferably 1 to 2 equivalents of a secondary amine (e.g., a compound of the formula: $HNR^{10}R^{11}$, etc.) or 1 to 10 equivalents, preferably 1 to 5 equivalents of a dimethylmethylene-ammonium salt (e.g., chloride, iodide, etc.), in an inert solvent, at room temperature to 80°C, for 1 to 48 hours. If desired, an equivalent amount to an excessive amount of an acid (e.g., mineral acids such as hydrochloric acid, etc.) may be added to the reaction system.

The inert solvent includes, for example, ethers, alcohols, nitriles, water, etc., which may be used either singly or as a suitable mixture of two or more species.

In the case that R^{10} and R^{11} each is C_{1-6} alkyl in the compound of the formula: $HNR^{10}R^{11}$, thus obtained compound (XI) is directly subjected to the reaction of step 12 without being subjected to the reaction of the next step 10.

(Step 10)

Compound (XI) is converted into its quaternary

amine salt, compound (XII).

After the previous step 9, the obtained compound (XI) is then reacted with 1 to 3 equivalents, preferably 1.1 to 1.5 equivalents of a C_{1-6} alkyl halide (e.g., methyl iodide, etc.) in an inert solvent (e.g., ketones, alcohols, etc.), at room temperature to a temperature for reflux, for 0.1 to 24 hours, preferably for 0.5 to 2 hours.

(Step 11)

Compound (XII) is subjected to amination to obtain compound (XIII).

The amination may be effected under the same reaction condition as that for the step 7. Concretely, for example, compound (XII) is stirred with 1 to 5 equivalents, preferably 1 to 3 equivalents of a compound of the formula: HNR^1R^2, in an inert solvent, at room temperature to 100° C, preferably at room temperature to 50° C, for 0.5 hours to one day. In general, 1 to 3 equivalents, preferably 1 to 2 equivalents of a base is added to the reaction system.

The "base" is the same as those mentioned in detail hereinabove for the step 1. Especially preferred are tertiary amines such as triethylamine, etc.; and alkali metal or alkaline earth metal carbonates, etc.

The inert solvent includes, for example, water, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, etc., which may be used either singly or as a suitable mixture of two or more species. Of those, preferred are acetonitrile, DMF, acetone, ethanol, etc.

Preferably, compound (XII) is stirred with 1 to 2 equivalents of a compound of the formula: HNR^1R^2, and 1 to 3 equivalents of a base (e.g., potassium carbonate, triethylamine, etc.), in an inert solvent (e.g.,

acetonitrile, DMF, etc.), at room temperature to 50°C, for 10 hours to one day.

(Step 12)

Compound (XIII) is subjected to reduction to obtain compound (XIV) via compound (XIIIa).

The reduction may be effected in any *per se* known manner, for example, according to the methods described in Organic Functional Group Preparations mentioned above, etc. Concretely, for example, (1) compound (XIII) is reacted with a metal hydride, (2) compound (XIII) is reacted with a metal, or (3) compound (XIII) is subjected to catalytic reduction.

In the above reaction (1), compound (XIII) is reacted with 1 to 20 equivalents, preferably 2 to 6 equivalents of a metal hydride in an inert solvent.

The "metal hydride" includes, for example, lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium borohydride cyanide, diborane, dibutyl aluminum hydride, etc.

The inert solvent is preferably ethers when lithium aluminum hydride is used, but is preferably alcohols when sodium borohydride is used.

The reaction temperature varies, depending on the metal hydride used, but, in general, may fall between -70 and 100°C, preferably between 0 and 80°C.

The reaction time falls between 0.1 and 24 hours, preferably between 0.5 and 12 hours.

In the above reaction (2), compound (XIII) is reacted with an excessive amount, preferably 1 to 100 equivalents of a metal (e.g., zinc powder) in an inert solvent at room temperature to 100°C for 1 to 24 hours. In the reaction (2), as the case may be, the reduction may be further promoted to directly give compound (XIV).

The inert solvent includes, for example, organic acids (e.g., acetic acid, etc.), ethers, etc., which

may be used either singly or as a suitable mixture of two or more species.

In the above reaction (3), compound (XIII) is reacted with a catalytic amount of a metal catalyst (e.g., Raney nickel, platinum oxide, palladium metal, palladium-carbon, etc.) in an inert solvent (e.g., alcohols, etc.), at room temperature to 100°C, under a hydrogen pressure of 1 to 100 atmospheres, for 1 to 48 hours. If desired, a catalytic amount to an excessive amount of an organic acid (e.g., acetic acid, etc.) or a mineral acid (e.g., perchloric acid, hydrochloric acid, etc.) may be added to the reaction system. In the reaction (3), as the case may be, the reduction may be further promoted to directly give compound (XIV).

The compound (XIIIa) obtained herein is subjected to reductive dehydration to give compound (XIV).

The reductive dehydration may be effected in any *per se* known manner, for example, through catalytic reduction or using an organic silyl reagent.

For the catalytic reduction, for example, it is preferred that compound (XIIIa) is reacted with a catalytic amount of a metal catalyst (e.g., Raney nickel, platinum oxide, palladium metal, palladium-carbon, etc.) in an inert solvent (e.g., alcohols, etc.) under a hydrogen pressure of 1 to 100 atmospheres, at room temperature to 100°C, for 1 to 48 hours. If desired, a catalytic amount to an excessive amount of an organic acid (e.g., acetic acid, etc.) or a mineral acid (e.g., perchloric acid, hydrochloric acid, etc.) may be added to the reaction system.

In the method of using an alkylsilane reagent, for example, compound (XIIIa) is reacted with an alkylsilane reagent (e.g., triethylsilane, phenyldimethylsilane, etc.) and an acid (e.g., organic acids such as trifluoroacetic acid, etc.), in the absence or presence of an inert solvent (e.g.,

halogenated hydrocarbons), at 0 to 100°C, preferably at 0 to 30°C, for 10 minutes to 24 hours.

The amount of the alkylsilane reagent to be used is 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to the compound (XIIIa).

The amount of the acid to be used is a catalytic amount to an excessive amount, preferably 1 to 5 equivalents, relative to the compound (XIIIa).

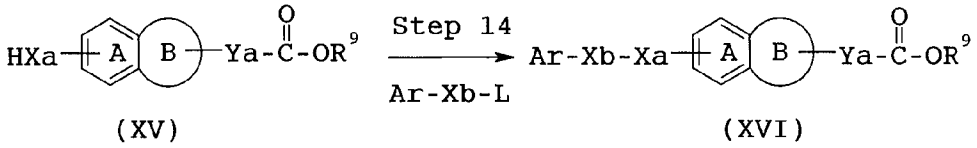
(Step 13)

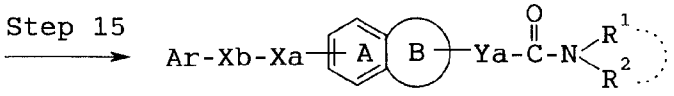
In the case that W is a protective group in compound (XIV), compound (XIV) is subjected to deprotection to obtain compound (IIb).

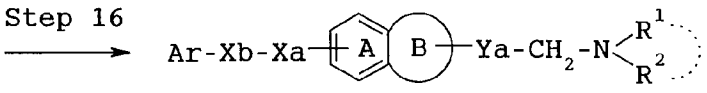
The deprotection may be effected under the same reaction condition as that for the step 4.

Process 2

Scheme 5







(Step 14)

Compound (XV) is subjected to alkylation or acylation to obtain compound (XVI).

Compound (XV) can be obtained by subjecting compound (III) wherein W is a hydrogen to

esterification in any *per se* known manner.

The alkylation and the acylation may be effected in the same manner as in the step 1.

(Step 15)

Compound (XVI) is subjected to hydrolysis in any *per se* known manner, and then amidation to obtain compound (XVII).

The amidation may be effected in the same manner as in the step 2.

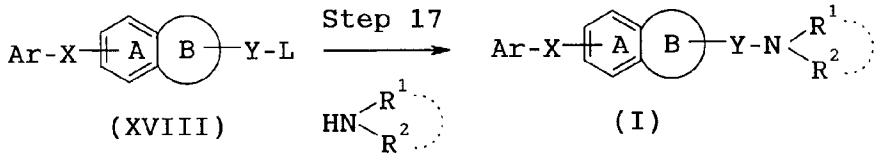
(Step 16)

Compound (XVII) is subjected to reduction to obtain compound (Ib).

The reduction may be effected in the same manner as in the step 3.

Process 3

Scheme 6



(XVIII) (I)

In the formula, L represents a leaving group.

The "leaving group" for L are the same as those mentioned hereinabove.

(Step 17)

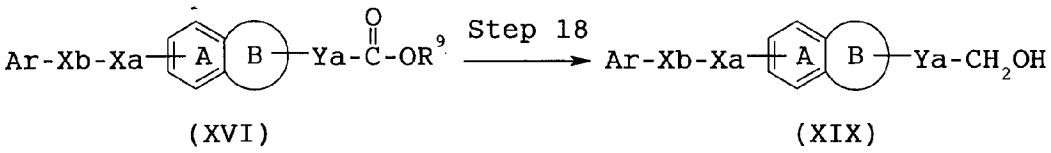
Compound (XVIII) is subjected to amination to obtain compound (I).

Compound (XVIII) can be produced with ease according to any known methods, for example, a method of scheme 7 mentioned below.

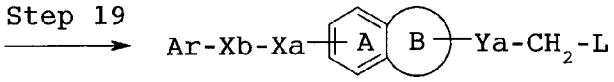
The amination may be effected in the same manner

as in the step 7.

Scheme 7



(XVI) (XIX)



(XVIIIa)

(Step 18)

Compound (XVI) is subjected to reduction to obtain compound (XIX).

The reduction may be effected in the same manner as in the step 5.

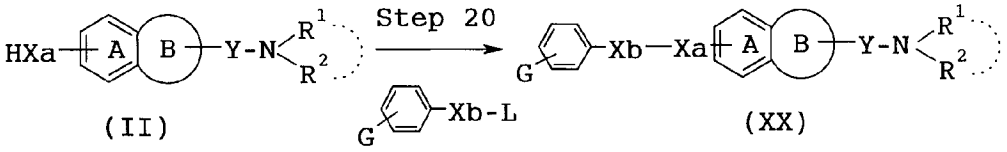
(Step 19)

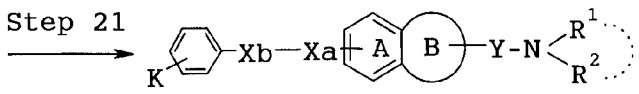
A leaving group is introduced into compound (XIX) to obtain compound (XVIIIa).

The introduction of the leaving group may be effected in the same manner as in the step 6.

Process 4

Scheme 8





(Ic)

In the formula, K represents an aromatic group

which may be substituted; and G represents a halogen atom (e.g., bromo, iodo), or a trifluoromethanesulfonyloxy.

For the "aromatic group which may be substituted" for K, referred to is the same as those mentioned hereinabove for the "aromatic group which may be substituted" for Ar'.

(Step 20)

Compound (II) is subjected to the same reaction as in the step 1 to obtain compound (XX).

(Step 21)

Compound (XX) is subjected to aryl-coupling reaction to obtain compound (Ic).

The aryl-coupling reaction may be effected in any *per se* known manner, for example, according to the methods described in Acta. Chemica Scandinavia, 221-230 (1993), etc. Concretely, for example, compound (XX) is reacted with 1 to 2 equivalents of an aryl metal compound and 1 to 10 equivalents of a base, in the presence of 0.01 to 1 equivalent, preferably 0.01 to 0.5 equivalents of a transition metal catalyst, in an inert solvent, at room temperature to 150°C, preferably at 80 to 150°C, for 1 to 48 hours.

The "aryl metal compound" includes, for example, aryl-boric acid derivatives, aryl-zinc derivatives, etc.

The "base" includes, for example, an aqueous solution of sodium carbonate, sodium hydrogencarbonate or the like.

The "transition metal catalyst" includes, for example, palladium catalysts, nickel catalysts, etc. The "palladium catalysts" include, for example, tetrakis(triphenylphosphine)palladium(0), palladium acetate, bis(triphenylphosphine)palladium(II) chloride, palladium-carbon, etc. The "nickel catalysts" include,

for example, tetrakis(triphenylphosphine)nickel(0), etc.

The inert solvent includes, for example, water, alcohols, aromatic solvents, etc., which may be used either singly or as a suitable mixture of two or more species. Preferred are water, ethanol, toluene, etc., which are used either singly or as a suitable mixture of two or more species.

Where the intermediates produced in those Processes 1 to 4 include optical isomers, any known methods of obtaining such "optical isomers of those intermediates" are employable herein. For example, the optical isomers may be derived from optically-active compounds, or racemates may be subjected to optical resolution or asymmetric synthesis.

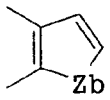
For the "optical resolution", referred to is the same as the optical resolution to be mentioned hereinafter.

The "asymmetric synthesis" may be effected in any *per se* known manner, including, for example, asymmetric reduction, asymmetric oxidation, asymmetric alkylation, etc. These reactions may be attained, for example, according to the methods described in Shin-Jikken Kagaku Koza, 26 (1992), edited by the Chemical Society of Japan and published by Maruzen Co., etc. Of those, preferred is asymmetric reduction.

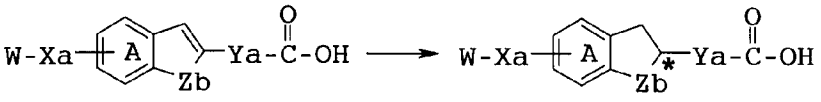
The "asymmetric reduction" includes, for example, reduction using asymmetric metal hydrides, asymmetric hydrogenation, etc. Preferred is asymmetric hydrogenation. The "asymmetric hydrogenation" includes, for example, a reaction using asymmetric metal catalysts. One embodiment of the asymmetric hydrogenation is effected in the presence of transition metal/optically-active phosphine complexes.

For example, compounds (III), (IV), (V), (VI), (VII), (XVI) and (XVII) produced in any of Processes 1

to 4, wherein each Ring B is a ring of the formula:

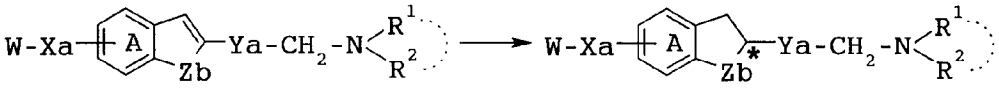


wherein Zb has the same meaning as Z, are subjected to asymmetric hydrogenation to obtain the corresponding optical isomers, respectively.



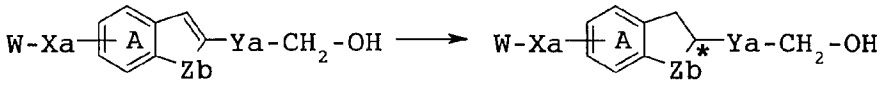
(IIIb) (IIIc)

(IVb) (IVc)

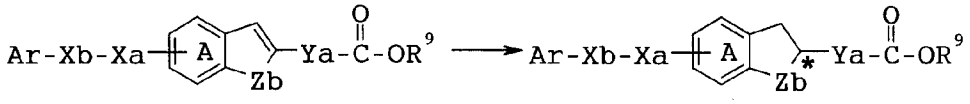


(Vb) (Vc)

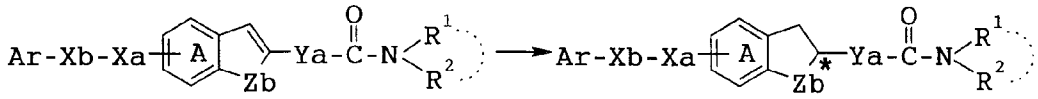
(VIb) (VIc)



(VIIb) (VIIc)



(XVIb) (XVIc)



(XVIIb) (XVIIc)

In those formulae, * indicates the position of the

asymmetric carbon, and the other symbols have the same meanings as above.

As one example of the "asymmetric hydrogenation", mentioned is a method of reacting compound (IIIb), (IVb), (Vb), (VIb), (VIIb), (XVIb) or (XVIIb) with approximately 0.00001 to 1 equivalent, preferably approximately 0.001 to 0.1 equivalents of a transition metal/optically-active phosphine complex, in an inert solvent, at room temperature to 100°C, preferably at about 50 to 80°C, under a hydrogen pressure of 5 to 100 kg/cm^2, preferably from 50 to 100 kg/cm^2, for 1 to 48 hours, preferably for 1 to 6 hours, to obtain compound (IIIc), (IVc), (Vc), (VIc), (VIIc), (XVIc) or (XVIIc), respectively.

The concentration of the compound (IIIb), (IVb), (Vb), (VIb), (VIIb), (XVIb) or (XVIIb) in the reaction system is 1 to 1000 mg/ml, preferably 50 to 300 mg/ml.

If desired, a suitable amount of a Lewis acid (e.g., boron trifluoride-ether complex, aluminum chloride, titanium tetrachloride, cobalt chloride, etc.) or a mineral acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, etc.) may be added to the reaction system.

The "transition metal" of the "transition metal/optically-active phosphine complex" includes, for example, ruthenium, rhodium, iridium, palladium, nickel, etc. Of those, preferred is ruthenium.

The optically-active phosphine of the "transition metal/optically-active phosphine complex" includes two optical isomers of (R) configuration and (S) configuration. Either one of the two optical isomers of (R) configuration and (S) configuration is used for the asymmetric reduction to selectively obtain the intended optical isomer product.

Examples of the "optically-active phosphine" are (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(R)-

(BINAP)], (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(S)-(BINAP)], (R)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl [(R)-(p-tolyl-BINAP)], (S)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl [(S)-(p-tolyl-BINAP)] (see JP-A-61-63690); (R)-2,2'-bis[di-(3,5-dimethylphenyl)phosphino]-1,1'-binaphthyl [(R)-(3,5-xylyl-BINAP)], (S)-2,2'-bis[di-(3,5-dimethylphenyl)phosphino]-1,1'-binaphthyl [(S)-(3,5-xylyl-BINAP)] (see JP-A-3-255090); (R)-2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [(R)-(H_8-BINAP)], (S)-2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [(S)-(H_8-BINAP)] (see JP-A-4-139140), etc.

The above "(R)" and "(S)" each indicates the absolute configuration in that optically-active phosphine.

The "transition metal/optically-active phosphine complex" may additionally have, as ligands, a halogen (e.g., chloro, etc.), an amine (e.g., triethylamine, etc.), an organic acid (e.g., acetic acid, etc.), a C_{6-10} aryl (e.g., benzene, etc.), etc.

After having been prepared, the "transition metal/optically-active phosphine complex" may be directly used in the reaction without being isolated or purified.

"Ruthenium/optically-active phosphine complexes" which are preferred examples of the "transition metal/optically-active phosphine complex" each are composed of ruthenium and either one, optically-active (R)- or (S)-phosphine compound, and include, for example, the following:

Bis[[(R)- or (S)-[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]]dichlororuthenium]triethylamine (referred to as $[RuCl_2[(R)\text{- or }(S)\text{-(BINAP)}]]_2NEt_3$);

Bis[[(R)- or (S)-[2,2'-bis(di-p-tolylphosphino)-

1,1'-binaphthyl]]dichlororuthenium]triethylamine (referred to as [$RuCl_2$[(R)- or (S)-(p-tolyl-BINAP)]]$_2NEt_3$);

Bis[[(R)- or (S)-[2,2'-bis(di-(3,5-dimethylphenyl)phosphino)-1,1'-binaphthyl]]dichlororuthenium]triethylamine (referred to as [$RuCl_2$[(R)- or (S)-(3,5-xylyl-BINAP)]]$_2NEt_3$);

Bis[[(R)- or (S)-[2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl]]dichlororuthenium]triethylamine (referred to as [$RuCl_2$[(R)- or (S)-(H_8-BINAP)]]$_2NEt_3$);

[(R)- or (S)-[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]]ruthenium diacetate (referred to as $Ru(CH_3CO_2)_2$[(R)- or (S)-(BINAP)]);

[(R)- or (S)-[2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl]]ruthenium diacetate (referred to as $Ru(CH_3CO_2)_2$[(R)- or (S)-(p-tolyl-BINAP)]);

[(R)- or (S)-[2,2'-bis(di-(3,5-dimethylphenyl)phosphino)-1,1'-binaphthyl]]ruthenium diacetate (referred to as $Ru(CH_3CO_2)_2$[(R)- or (S)-(3,5-xylyl-BINAP)]);

[(R)- or (S)-[2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl]]ruthenium diacetate (referred to as $Ru(CH_3CO_2)_2$[(R)- or (S)-(H_8-BINAP)]).

The inert solvent includes, for example, hydrocarbons, amides, aromatic solvents, ethers, halogenated hydrocarbons, alcohols, ketones, sulfoxides, nitriles, etc., which may be used either singly or as a suitable mixture of two or more species. Preferred are alcohols, and more preferred is ethanol.

The above "alcohols" includes, for example, methanol, ethanol, isopropanol, tert-butanol, etc.

The above "ethers" includes, for example, ethyl ether, tetrahydrofuran (THF), dioxane, 1,2-

dimethoxyethane, etc.

The above "halogenated hydrocarbons" includes, for example, dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, etc.

The above "aromatic solvents" includes, for example, benzene, toluene, xylene, pyridine, etc.

The above "hydrocarbons" includes, for example, hexane, pentane, cyclohexane, etc.

The above "amides" includes, for example, N,N'-dimethylformamide (DMF), N,N'-dimethylacetamide, N-methylpyrrolidone, etc.

The above "ketones" includes, for example, acetone, methyl ethyl ketone, etc.

The above "sulfoxides" includes, for example, dimethylsulfoxide (DMSO), etc.

The above "nitriles" includes, for example, acetonitrile, propionitrile, etc.

The above "esters" includes, for example, ethyl acetate, etc.

In the above-mentioned reactions where the starting compounds are substituted by any of amino, carboxy, hydroxy or carbonyl, those groups may be protected by ordinary protective groups which are generally used in peptide chemistry. The protective groups may be removed after the reaction to give the intended products.

The amino-protecting group includes, for example, formyl , C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C_{1-6} alkyloxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl, etc.), C_{7-14} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, etc.), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, dimethyl-t-

butylsilyl, diethyl-t-butylsilyl, etc.), C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 substituents of halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.) or nitro, etc.

The carboxy-protecting group includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{7-11} aralkyl (e.g., benzyl, etc.), phenyl, trityl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, dimethyl-t-butylsilyl, diethyl-t-butylsilyl, etc.), a C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 substituents of halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.) or nitro, etc.

The hydroxy-protecting group includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, C_{7-10} aralkyl (e.g., benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, dimethyl-t-butylsilyl, diethyl-t-butylsilyl, etc.), C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 substituents of halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-6} alkyl (e.g., methyl, ethyl, propyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.) or nitro, etc.

The carbonyl-protecting group includes, for example, cyclic acetals (e.g., 1,3-dioxorane, etc.), acyclic acetals (e.g., di-C_{1-6} alkylacetals, etc.), etc.

Those protective groups may be removed by any *per se* known methods, for example, the methods described in Protective Groups in Organic Synthesis, published by

John Wiley and Sons, 1980, etc. For example, the method of removing these protective groups, includes the methods using acids, bases, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.; and reduction, etc.

Compound (I) can be isolated and purified by any known procedures, for example, through solvent extraction, ph adjustment, redistribution, crystallization, recrystallization, chromatography, etc. The starting compounds and intermediates and their salts for compound (I) can also be isolated and purified according to the same known procedures as above, but without any isolation procedure, they may be used in the next step while they are in reaction mixtures.

Compound (I) may also be in the form of hydrates or non-hydrates thereof.

Where compound (I) includes optical isomers, stereoisomers, regio isomers and rotational isomers, those are within the scope of compound (I), and can be isolated as their single compound through *per se* known synthesis or separation. For example, where optical isomers of compound (I) exist, those resolved from their mixtures through optical resolution are within the scope of compound (I).

The optical isomers can be produced in any *per se* known manner. Concretely, optically active synthetic intermediates or mixtures of racemate of the final product are subjected to ordinary optical resolution to give the corresponding optical isomers.

For the optical resolution, employable are any *per se* known methods, such as a fractional recrystallization method, a chiral column method, a diastereomer method, etc.

1) Fractional Recrystallization

The method which comprises allowing a racemate to react with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.) to give a salt, which is then isolated through fractional recrystallization, followed by, when desired, subjecting the isolated compound to neutralization to obtain free optical isomers.

2) Chiral Column Method

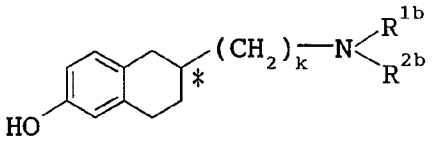
The method of separating a racemate or a salt thereof, which comprises utilizing a column for fractionating optical isomers (chiral column). In the case of liquid column chromatography, for example, a mixture of optical isomers is applied to a chiral column, such as ENANTIO-OVM (manufactured by Tosoh Corp.), CHIRAL SERIES (manufactured by Daicel Co.), etc., which is then eluted with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.), singly or a suitable mixture of them, to isolate the individual optical isomers. In case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Science Co.), etc. is used for the fractionation.

3) Diastereomer Method

A racemic mixture is chemically reacted with an optically-active reagent to give a mixture of diastereomer, which is subjected to ordinary separation (e.g., fractional recrystallization, chromatography, etc.) to give single compounds. The thus-isolated single compounds are then chemically processed, for example, through hydrolysis to thereby remove the optically-active reagent site from the compounds to

obtain optical isomers. For example, where compound (I) has a hydroxy group or a primary or secondary amino group in the molecule, it is condensed with an optically-active organic acid (e.g., MPTA [α-methoxy-α-(trifluoromethyl)phenyl-acetic acid], (-)-menthoxyacetic acid, etc.) or the like to give the corresponding ester-type or amide-type diastereomer. On the other hand, where compound (I) has a carboxylic acid group, it is condensed with an optically-active amine or alcohol reagent to give the corresponding amide-type or ester-type diastereomer. The thus-isolated diastereomer is then subjected to acidic or basic hydrolysis, through which it is converted into the optical isomer of the original compound.

In the above-mentioned reactions, an optical isomer of the compound of the formula:



wherein R^{1b} and R^{2b} each represents methyl or ethyl, k represents 1 or 2, and * indicates the position of the asymmetric carbon, or a salt thereof is a novel compound.

Compound (I) of the present invention has both an excellent inhibitory effect on amyloid-β protein production and/or secretion and an excellent stimulating effect on secreted form of amyloid precursor protein (sAPP) secretion, and thus is effective in preventing and/or treating neurodegenerative disorders, amyloid angiopathy, neurological disorders caused by cerebrovascular disorders (e.g., cerebral infarction, encephalorrhagia,

etc.), a head injury or an injury of spinal cord, etc. Compound (I') also has the inhibitory effect on amyloid-β protein production and/or secretion and stimulating effect on sAPP secretion.

In addition, compounds (I) and (I') have low toxicity. For example, in the experiment of acute toxicity, no mouse was dead by the oral administration of the compound obtained in Example 12 mentioned below a dose of more than 1000 mg/kg. Moreover, compounds (I) and (I') easily penetrate into the brain following the oral administration.

Therefor, compounds (I) and (I') are useful as safe medicines for preventing and/or treating neurodegenerative disorders, amyloid angiopathy, neurological disorders caused by cerebrovascular disorders (e.g., cerebral infarction, encephalorrhagia, etc.), a head injury or an injury of spinal cord, in mammals including human beings. They are also useful in ameliorating derangements (for example, depression, anxiety, compulsive neurosis, sleep disorders, etc.) caused by neurodegenerative disorders or neurological disorders. Of those, compounds (I) and (I') are preferably effective for neurodegenerative disorders such as Alzheimer's disease, Down's syndrome, senile dementia, Parkinson's disease, Creutzfeldt-Jacob disease, amyotrophic sclerosis on lateral fasciculus of spinal, diabetic neuropathy, Huntington's disease, multiple sclerosis, etc. Among others, preferred is neurodegenerative disorders to be coursed by amyloid-β protein (e.g., Alzheimer's disease, Down's syndrome, etc.), more preferred is Alzheimer's disease.

Compounds (I) and (I') may be used in combination with anti-dementia drugs (e.g., acetylcholinesterase inhibitor, etc.), and so forth.

Compounds (I) and (I') can be formulated into

pharmaceutical compositions by any *per se* known means. Directly or after having been formulated into pharmaceutical compositions along with suitable amounts of any pharmaceutically acceptable carriers, compounds (I) and (I') can be safely administered to mammals including human beings. For example, compound (I) or (I') can be mixed with suitable amounts of any desired, pharmaceutically-acceptable carriers in any *per se* known formulation processes to give tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, etc., which may be safely administered to mammals including human beings, either orally or non-orally (for example, topically, rectally, intravenously, etc.).

In the pharmaceutical composition of the present invention, the amount of compound (I) or (I') is 0.1 to 100 % by weight of the total weight of the composition. The dose of the composition varies depending on the subject to which the composition is administered, the administration route employed, the disorder of the subject, etc. For example, for the peroral composition for treating Alzheimer's disease, its dose may be about 0.1 to 500 mg/adult (weighing about 60 kg) or so, preferably about 1 to 100 mg/adult or so, more preferably 5 to 100 mg/adult or so, in terms of the active ingredient [compound (I) or (I')], and this may be administered once or several times a day.

Any ordinary organic and inorganic carrier substances that are generally used in formulating medicines are usable as the carriers for formulating the pharmaceutical compositions of the present invention. For example, employable are ordinary excipients, lubricants, binders, disintegrators, etc. for formulating solid preparations; and solvents,

solubilizers, suspending agents, isotonizing agents, buffers, soothing agents, etc. for formulating liquid preparations. If desired, further employable are other additives such as preservatives, antioxidants, colorants, sweeteners, adsorbents, wetting agents, etc.

The excipients include, for example, lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride, etc.

The lubricants include, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

The binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, carboxymethyl cellulose sodium, etc.

The disintegrators include, for example, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, L-hydroxypropyl cellulose, etc.

The solvents include, for example, water for injections, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc.

The solubilizers include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

The suspending agents include, for example, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.

The isotonizing agents include, for example,

glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

The buffers include, for example, liquid buffers of phosphates, acetates, carbonates, citrates, etc.

The soothing agents include, for example, benzyl alcohol, etc.

The preservatives include, for example, parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The antioxidants include, for example, sulfites, ascorbic acid, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

The invention will be described in more detail hereinunder, with reference to Reference Examples, Examples, and Test Examples, which, however, are to concretely demonstrate the invention but not to restrict the scope of the invention. Various changes and modifications can be made within the range that does not deviate the scope of the invention.

"Room temperature" as referred to in the following Reference Examples and Examples is meant to indicate a temperature falling between 0°C and 30°C. For removing water from the organic solution used therein, employed were anhydrous magnesium sulfate or anhydrous sodium sulfate. Unless otherwise specifically indicated, "%" is by weight.

The IR absorption spectra mentioned below were measured in a diffused reflection method using a Fourier transform infrared spectrophotometer.

The meanings of the abbreviations used hereinunder are as follows:

s: singlet
d: doublet
t: triplet
q: quartet
m: multiplet

br: broad
J: coupling constant
Hz: Hertz
$CDCl_3$: deuterated chloroform
THF: tetrahydrofuran
DMF: N,N-dimethylformamide
DMSO: dimethylsulfoxide
WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
^1H NMR: proton nuclear magnetic resonance spectrum (generally measured as the free form of each sample in $CDCl_3$)
IR: infrared absorption spectrum

Reference Example 1

6-Methoxy-2-piperidinomethyl-1-tetralone hydrochloride

N-(6-Methoxy-1-oxo-2-tetralinyl)methyl-N,N,N-trimethylammonium iodide (1.137 g), piperidine (0.36 ml) and triethylamine (0.55 ml) were added to acetonitrile (300 ml). The reaction mixture was stirred at room temperature for 2 hours, and then concentrated. Water was added to this, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/2), and then processed with a solution of 4 N hydrochloric acid-ethyl acetate. The resulting hydrochloride was recrystallized from methanol-ethyl acetate to obtain the entitled compound (0.586 g).

m.p.: 182-183° C.

Compounds of the following Reference Examples 2 and 3 were obtained in the same manner as in Reference

Example 1.

Reference Example 2

2-(N-Benzylamino)methyl-6-methoxy-1-tetralone hydrochloride

m.p.: 166-169° C.

Solvent for recrystallization: methanol-ethyl acetate

Reference Example 3

2-(N,N-Dibenzylamino)methyl-6-methoxy-1-tetralone

m.p.: 91-92° C.

Solvent for recrystallization: ethyl acetate-diisopropyl ether

Reference Example 4

2-(N,N-Dimethylamino)methyl-7-methoxytetralin hydrochloride

1 N Sodium hydroxide was added to 2-(N,N-dimethylamino)methyl-7-methoxy-1-tetralone hydrochloride (8.46 g) to convert it into a free compound, which was extracted with ethyl acetate. The extract was dried, and then concentrated. Sodium borohydride (2.32 g) was added to a methanol solution (150 ml) of the resulting residue, with cooling with ice, which was then stirred at room temperature for 12 hours. Water was added to the reaction mixture, which was concentrated under reduced pressure, and then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. Concentrated hydrochloric acid (6.4 g) and 10% palladium-carbon (0.7 g) were added to an ethanol solution (100 ml) of the resulting residue, which was thus catalytically reduced under a hydrogen pressure of 5 atmospheres at 60° C for 8 hours. The catalyst was removed from the reaction mixture through filtration, and the filtrate was concentrated. The residue was recrystallized from